FOX

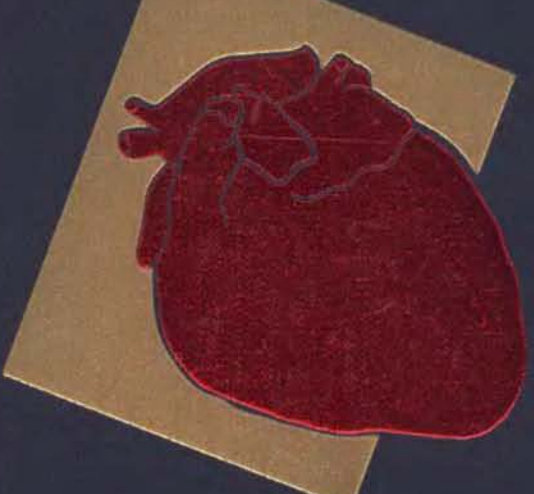
SISSON

MOÏSE

SECOND EDITION

TEXTBOOK OF CANINE AND FELINE Cardiology

Principles and Clinical Practice



TEXTBOOK OF CANINE AND FELINE Cardiology

Principles and Clinical Practice

SECOND EDITION

Philip R. Fox, D.V.M., M.Sc.
Diplomate, American and European College of Veterinary Internal Medicine (Cardiology)
Diplomate, American College of Veterinary Emergency and Critical Care
Astor Chair of Comparative Medicine
Director, Caspary Research Institute of The Animal Medical Center
Cardiologist, Department of Medicine
Bobst Hospital of The Animal Medicine Center
New York, New York

David Sisson, D.V.M.
Diplomate, American College of Veterinary Internal Medicine (Cardiology)
Associate Professor of Cardiology
Director, Cardiology Service
University of Illinois
College of Veterinary Medicine
Urbana, Illinois

N. Sydney Moïse, D.V.M., M.S.
Diplomate, American College of Veterinary Internal Medicine (Cardiology and Internal Medicine)
Cardiologist, Veterinary Medical Teaching Hospital
Professor of Medicine, Department of Clinical Sciences
Cornell University
College of Veterinary Medicine
Ithaca, New York

W.B. SAUNDERS COMPANY
A Division of Harcourt Brace & Company
Philadelphia London Toronto Montreal Sydney Tokyo

W.B. SAUNDERS COMPANY
A Division of Harcourt Brace & Company

The Curtis Center
Independence Square West
Philadelphia, Pennsylvania 19106

Library of Congress Cataloging-in-Publication Data

Textbook of canine and feline cardiology: principles and clinical practice—2nd ed. / [edited by] Philip R. Fox, David Sisson, N. Sydney Moïse.

p. cm.

Rev. ed. of: Canine and feline cardiology. 1988

Includes bibliographical references and index.

ISBN 0–7216–4044–3

1. Dogs—Diseases. 2. Cats—Diseases. 3. Veterinary cardiology.
I. Fox, Philip R. II. Sisson, David. III. Moïse, N. Sydney.
IV. Canine and feline cardiology.

[DNLM: 1. Dog Diseases. 2. Cat Diseases. 3. Cardiovascular Diseases—veterinary. SF 992.C37 T355 1999]
SF992.C37C36 1999

636.7′089612—dc20

DNLM/DLC 96–22328

TEXTBOOK OF CANINE AND FELINE CARDIOLOGY: Principles and Clinical Practice ISBN 0–7216–4044–3

Copyright © 1999, 1988 by W.B. Saunders Company.

All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the publisher.

Printed in the United States of America.

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Contributors

Clarke E. Atkins, D.V.M.
Diplomate, American College of Veterinary Internal Medicine (Cardiology and Internal Medicine); Professor of Medicine and Cardiology, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina
Cardiac Manifestations of Systemic and Metabolic Disease

Sanford P. Bishop, D.V.M., Ph.D.
Diplomate, American College of Veterinary Internal Medicine (Cardiology), American College of Veterinary Pathology; Professor of Pathology, Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama
Embryonic Development; Cardiovascular Anatomy; Necropsy Techniques for the Heart and Great Vessels

John D. Bonagura, D.V.M., M.S.
Diplomate, American College of Veterinary Internal Medicine (Cardiology and Internal Medicine); Gilbreath-McLorn Professor of Veterinary Cardiology, Department of Veterinary Medicine and Surgery, University of Missouri College of Veterinary Medicine, Columbia; Cardiologist, Veterinary Medical Teaching Hospital, Columbia, Missouri
Pulmonary Edema; Congenital Heart Disease

Janice M. Bright, D.V.M., M.S.
Diplomate, American College of Veterinary Internal Medicine (Cardiology and Internal Medicine); Associate Professor, Department of Clinical Sciences, Colorado State University Veterinary Teaching Hospital, Fort Collins, Colorado
Nuclear Imaging, Computed Tomography, and Magnetic Resonance Imaging of the Heart

John D. Broussard, D.V.M.
Diplomate, American College of Veterinary Internal Medicine; Internist, Department of Medicine, Bobst Hospital of The Animal Medical Center, New York, New York
Hyperthyroidism and Other High Output States

James W. Buchanan, D.V.M.
Professor of Cardiology, University of Pennsylvania School of Veterinary Medicine, Philadelphia, Pennsylvania
Prevalence of Cardiovascular Disorders

Clay A. Calvert, D.V.M.
Professor, Department of Small Animal Medicine and Surgery, University of Georgia College of Veterinary Medicine, Athens, Georgia
Myocardial Diseases of Dogs; Canine Heartworm Disease

Dennis T. Crowe, Jr., D.V.M.
Diplomate, American College of Veterinary Surgeons, American College of Veterinary Emergency and Critical Care; Georgia Veterinary Specialists Emergency and Critical Care, Alpharetta, Georgia
Cardiopulmonary and Cerebral Resuscitation

Kenneth H. Dangman, M.D., Ph.D.
Clinical Fellow, Baystate Medical Center, Tufts University, School of Medicine, Springfield, Massachusetts
Electrophysiologic Mechanisms for Arrhythmias

Gregory B. Daniel, D.V.M., M.S.
Diplomate, American College of Veterinary Radiology; Associate Professor and Head, Radiology, Department of Small Animal Clinical Science, University of Tennessee College of Veterinary Medicine, Knoxville, Tennessee
Nuclear Imaging, Computed Tomography, and Magnetic Resonance Imaging of the Heart

Peter G. G. Darke, B.V.Sc., Ph.D., D.V.R., D.V.C., M.R.C.V.S.
Diplomate, European College of Veterinary Internal Medicine (Cardiology); Department of Veterinary Clinical Studies, Royal (Dick) School of Veterinary Studies, University of Edinburgh, Edinburgh, United Kingdom
Acquired Valvular Heart Disease in Dogs and Cats

Jennifer J. Devey, D.V.M.
Diplomate, American College of Veterinary Emergency and Critical Care; South Paws Veterinary Referral Center, Springfield, Virginia
Cardiopulmonary and Cerebral Resuscitation

Ray Dillon, D.V.M., M.S.
Diplomate, American College of Veterinary Internal Medicine; Jack O. Rash Professor of Medicine, Department of Small Animal Surgery and Medicine, Auburn University, College of Veterinary Medicine, Auburn, Alabama
Feline Heartworm Disease

Stephen J. Ettinger, D.V.M.
Diplomate, American College of Veterinary Internal Medicine (Internal Medicine and Cardiology); California Animal Hospital, Los Angeles, California
The Physical Examination

Howard E. Evans, D.V.M., Ph.D.
Professor Emeritus, Department of Biomedical Sciences, Cornell University College of Veterinary Medicine, Ithaca, New York
Cardiovascular Anatomy

George E. Eyster, V.M.D., M.S.
Diplomate, American College of Veterinary Surgeons; Professor, Department of Small Animal Clinical Sciences, Michigan State University College of Veterinary Medicine, East Lansing; MSU Veterinary Clinic, East Lansing, Michigan
Basic Cardiovascular Surgery and Procedures

Philip R. Fox, D.V.M., M.Sc.
Diplomate, American and European College of Veterinary Internal Medicine (Cardiology); American College of Veterinary Emergency and Critical Care; Astor Chair of Comparative Medicine; Director, Caspary Research Institute of The Animal Medical Center; Cardiologist, Department of Medicine, Bobst Hospital of The Animal Medical Center, New York, New York
Cardiovascular Anatomy; The History; Electrocardiography; Echocardiography and Doppler Imaging; Diagnosis and Management of Feline Arrhythmias; Cardiopulmonary and Cerebral Resuscitation; Feline Cardiomyopathies; Nutrition and Management of Cardiovascular Disease; Hyperthyroidism and Other High Output States; Systemic Hypertension: Recognition and Treatment; Cardiovascular Pathology

Robert L. Hamlin, D.V.M., Ph.D.
Diplomate, American College of Veterinary Internal Medicine (Cardiology and Internal Medicine); Stanton Youngberg Professor of Veterinary Biosciences, Department of Veterinary Biosciences, The Ohio State University College of Veterinary Medicine, Columbus, Ohio
Normal Cardiovascular Physiology; Pathophysiology of the Failing Heart

Neil K. Harpster, V.M.D.
Diplomate, American College of Veterinary Internal Medicine (Cardiology); Adjunct Professor, Tufts University School of Veterinary Medicine, Boston; Director of Cardiology, Angell Memorial Animal Hospital, Jamaica Plain, Massachusetts
Diagnosis and Management of Feline Arrhythmias

Steven C. Haskins, D.V.M., M.S.
Diplomate, American College of Anesthesiology, American College of Veterinary Emergency and Critical Care; Department of Veterinary Surgery and Radiology, University of California School of Veterinary Medicine, Davis; Veterinary Medical Teaching Hospital, Davis, California
Treatment of Shock

John A. E. Hubbell, D.V.M., M.S.
Diplomate, American College of Veterinary Anesthesiologists; Associate Professor and Assistant Dean for Academic Affairs, The Ohio State University College of Veterinary Medicine, Columbus, Ohio
Anesthesia and the Heart

Bruce W. Keene, D.V.M., M.Sc.
Diplomate, American College of Veterinary Internal Medicine (Cardiology); Associate Professor of Cardiology, North Carolina State University College of Veterinary Medicine, Raleigh, North Carolina
Nutrition and Management of Cardiovascular Disease

Mark D. Kittleson, D.V.M., Ph.D.
Diplomate, American College of Veterinary Internal Medicine (Cardiology); Professor, Department of Medicine and Epidemiology, University of California School of Veterinary Medicine, Davis, California
Management of Heart Failure: Principles of Treatment, Therapeutic Strategies, and Pharmacology

Clarence Kvart, D.V.M., Ph.D.
Diplomate, European College of Veterinary Internal Medicine (Cardiology); Associate Professor, Department of Animal Physiology, Veterinary Faculty, Swedish University of Agricultural Sciences, Uppsala, Sweden
Acquired Valvular Heart Disease in Dogs and Cats

Linda B. Lehmkuhl, D.V.M., M.S.
Diplomate, American College of Veterinary Internal Medicine (Cardiology); Assistant Professor, The Ohio State University College of Veterinary Medicine; Staff Cardiologist, The Ohio State University Veterinary Teaching Hospital, Columbus, Ohio
Congenital Heart Disease

Meryl P. Littman, V.M.D.
Diplomate, American College of Veterinary Internal Medicine; Associate Professor of Medicine, Chief, Section of Medicine, University of Pennsylvania School of Veterinary Medicine, Philadelphia, Pennsylvania
Systemic Hypertension: Recognition and Treatment

Si-Kwang Liu, D.V.M., Ph.D.
Associate Director, Caspary Research Institute; Senior Pathologist, Department of Pathology, The Animal Medical Center, New York, New York
Cardiovascular Pathology

Peter F. Lord, B.V.Sc., F.R.C.V.S.
Diplomate, American College of Veterinary Radiology; Professor, Department of Clinical Radiology, Veterinary Faculty, Swedish University of Agricultural Sciences, Uppsala, Sweden
Radiology

Diane E. Mason, D.V.M., M.S.
Diplomate, American College of Veterinary Anesthesiologists; Clinical Instructor, Department of Anatomy and Physiology, Kansas State University, College of Veterinary Medicine, Manhattan, Kansas
Anesthesia and the Heart

John W. McCall, B.Sc., M.Sc., Ph.D.
Professor of Parasitology, Department of Parasitology, University of Georgia College of Veterinary Medicine, Athens, Georgia

Canine Heartworm Disease

Matthew Miller, D.V.M., M.S.
Diplomate, American College of Veterinary Medicine (Cardiology); Associate Professor, Department of Small Animal Medicine and Surgery, Texas A&M University College of Veterinary Medicine; Staff Cardiologist, Texas Veterinary Medical Center and Veterinary Teaching Hospital, College Station; Adjunct Assistant Professor of Pediatric Cardiology, Baylor College of Medicine, Houston, Texas

Infective Endocarditis; Nutrition and Management of Cardiovascular Disease

Michael S. Miller, V.M.D., M.S.
Diplomate, American Board of Veterinary Practitioners (Canine and Feline); Director, Cardiology-Ultrasound Referral Service, Thornton, Pennsylvania

Electrocardiography

N. Sydney Moïse, D.V.M., M.S.
Diplomate, American College of Veterinary Internal Medicine (Cardiology and Internal Medicine); Cardiologist, Veterinary Medical Teaching Hospital; Professor of Medicine, Department of Clinical Sciences, Cornell University College of Veterinary Medicine, Ithaca, New York

Cardiovascular Anatomy; Echocardiography and Doppler Imaging; Pharmacology and Pharmacokinetics of Antiarrhythmic Drugs; Diagnosis and Management of Canine Arrhythmias; Pacemaker Therapy

William W. Muir, III, D.V.M., M.S., Ph.D.
Diplomate, American College of Veterinary Anesthesiologists; American College of Veterinary Emergency and Critical Care; Professor, Department of Veterinary Clinical Sciences, The Ohio State University College of Veterinary Medicine, Columbus, Ohio

Pharmacology and Pharmacokinetics of Antiarrhythmic Drugs

Michael R. O'Grady
Diplomate, American College of Veterinary Internal Medicine (Cardiology and Internal Medicine); Associate Professor, Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada

Myocardial Disease of Dogs

Mark E. Peterson, D.V.M.
Diplomate, American College of Veterinary Internal Medicine; Associate Director, Caspary Research Institute; Head, Division of Endocrinology, Department of Medicine, Bobst Hospital of The Animal Medical Center, New York, New York

Hyperthyroidism and Other High Output States

Paul D. Pion, D.V.M.
Diplomate, American College of Veterinary Internal Medicine (Cardiology); President, Veterinary Information Network; private practice, Davis, California

Nutrition and Management of Cardiovascular Disease

Clarence A. Rawlings, D.V.M., Ph.D.
Diplomate, American College of Veterinary Surgeons; Professor and Head, Department of Small Animal Medicine, University of Georgia College of Veterinary Medicine, Athens, Georgia

Canine Heartworm Disease

John E. Rush, D.V.M., M.S.
Diplomate, American College of Veterinary Internal Medicine (Cardiology); American College of Veterinary Emergency and Critical Care; Associate Professor, Clinical Cardiologist, Co-Director of ICU/Emergency Services, Tufts University School of Veterinary Medicine, North Grafton, Massachusetts

Syncope and Episodic Weakness

Richard A. Sams, Ph.D.
Professor, Department of Veterinary Clinical Sciences, The Ohio State University College of Veterinary Medicine, Columbus, Ohio

Pharmacology and Pharmacokinetics of Antiarrhythmic Drugs

William C. Shoemaker, M.D.
Professor of Anesthesia and Surgery, University of Southern California, Los Angeles, California

Pathophysiology and Monitoring of Shock

David Sisson, D.V.M.
Diplomate, American College of Veterinary Medicine (Cardiology); Associate Professor of Cardiology, Director, Cardiology Service, University of Illinois College of Veterinary Medicine, Urbana, Illinois

The Physical Examination; Cardiac Catheterization and Angiocardiography; Management of Heart Failure: Principles of Treatment, Therapeutic Strategies, and Pharmacology; Acquired Valvular Heart Disease in Dogs and Cats; Infective Endocarditis; Myocardial Diseases of Dogs; Pericardial Disease and Cardiac Tumors

Francis W. K. Smith, Jr., D.V.M.
Diplomate, American College of Veterinary Internal Medicine (Internal Medicine and Cardiology); Clinical Assistant Professor, Department of Medicine, Tufts University School of Veterinary Medicine, North Grafton, Massachusetts; Chief of Medicine, Cardiopet Inc., Little Falls, New Jersey

Electrocardiography

David Spreng, D.V.M.
Associate Professor of Surgery, University of Bern Faculty of Veterinary Medicine, Bern, Switzerland

Cardiopulmonary and Cerebral Resuscitation

Peter F. Suter, D.V.M.
Former Professor of Veterinary Radiology and Internal Medicine, Department of Veterinary Medicine, Professor Emeritus, Faculty of Veterinary Medicine, University of Zurich; Former Director, Small Animal Veterinary Medical Clinic and Division of Radiology, Kant. Tierspital, University of Zurich, Zurich, Switzerland

Radiology

William P. Thomas, D.V.M.

Diplomate, American College of Veterinary Internal Medicine (Cardiology); Professor, Department of Medicine and Epidemiology, University of California School of Veterinary Medicine, Davis; Chief, Cardiology Service, Veterinary Medical Teaching Hospital, University of California, Davis, California

Cardiac Catheterization and Angiocardiography; Pericardial Disease and Cardiac Tumors

Larry P. Tilley, D.V.M.

Diplomate, American College of Veterinary Internal Medicine; Adjunct Professor, Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada; President, Vet Med Fax Consultation Services, Santa Fe, New Mexico

Electrocardiography

Wendy A. Ware, D.V.M., M.S.

Diplomate, American College of Veterinary Internal Medicine (Cardiology); Associate Professor, Departments of Veterinary Clinical Sciences and Veterinary Physiology and Pharmacology, Iowa State University College of Veterinary Medicine, Ames; Staff Cardiologist, Veterinary Teaching Hospital, Ames, Iowa

Pulmonary Edema

Preface

And I said of medicine, that this is an art which considers the constitution of the patient, and has principles of action and reasons in each case.

PLATO, 4TH CENTURY B.C.

He who has an absolutely clear insight into the immediate cause of an illness, must be considered preeminently capable of combating it.

HERMANNI BOERHAAVE, 1703

The young physician starts life with twenty drugs for each disease, and the old physician ends life with one drug for twenty diseases.

SIR WILLIAM OSLER, LATE 19TH CENTURY

The past 25 years have witnessed remarkable advances in the science and practice of cardiology. Barely a generation ago, clinical assessment was largely confined to auscultation, electrocardiography, phonocardiography, and radiography; angiography was the gold standard for anatomic diagnosis but was generally a province of referral institutions. Therapy often centered on furosemide, digitalis glycosides, propranolol, and a few other agents, and correction of congenital anomalies was the purview of surgeons. In contrast, today's clinical environment offers an impressive array of technologic advances. High resolution, noninvasive imaging has replaced invasive angiocardiography as the gold standard for morphologic diagnosis. A broad range of therapeutic options have become available, including a plethora of new cardiovascular drugs and related agents. Furthermore, nonsurgical interventional techniques are becoming widely introduced to correct certain congenital anomalies.

The exponential expansion of knowledge associated with these rapid changes presents unique challenges to the student, practitioner, and specialist. Since the first edition of *Canine and Feline Cardiology* was published in 1988, clinicians must increasingly divide their time between the burgeoning medical literature, keeping abreast of new and complex technologies, and a bewildering mountain of information. Accordingly, we intended *Textbook of Canine and Feline Cardiology: Principles and Clinical Practice,* 2nd edition, to be a complete, cutting-edge, and authoritative treatise of clinical cardiology. Toward this end, we enlisted some of the most notable leaders in the field, and focused their expertise into a comprehensive and usable source of definitive information.

Physicians have stated through antiquity that in order to provide optimal care, one must first understand the fundamental bases which underlie structure and function. Consequently, we have included the essential aspects of cardiac anatomy, phyisology, pathology, and pharmacology and synthesized these elements with discussions of diagnostic techniques and principles of therapy. In this fashion, we have attempted to bring together the "state of the art" into one practical source designed to bridge the gap between clinical cardiology and the empiric foundation on which such practice should be based.

To accomplish these goals we have organized this textbook as a multipurpose resource incorporating the best features of an atlas, a reference, and a clinical guide. In order to allow recent medical advances to be readily grasped, the text employs a practical and easy-to-use format, combined with detailed figures and extensive bibliographies. By this construct, the 2nd edition covers all clinical, diagnostic, and treatment facets of canine and feline cardiology. It begins with the anatomic and physiologic basis of cardiovascular structure and function; integrates these concepts with patient assessment, diagnostic methods, and examination; reviews abnormal cardiovascular function; discusses principles of therapy; details congenital and acquired cardiovascular diseases; and reviews salient cardiovascular surgery and anesthesia. Thus, it is our hope that this textbook will assist a broad range of students, practitioners, and specialists who are responsible for evaluating and treating the cardiac patient to do the right thing for the right reasons, and to do them dependably, consistently, and effectively.

A unique and notable aspect of this work emanates from the fact that it represents the comprehensive expertise of 50 cardiologists and allied specialists. As such, it represents the largest multi-authored cardiology textbook in the world. These contributors are not only international authorities in their respective fields but are also preeminent and thoughtful clinicians. We have made every effort to synthesize and integrate their extensive experience into a focused, systematic approach to provide the most advanced resource available on canine and feline cardiology.

I extend my deep appreciation to our numerous contributors who have generously shared their knowledge, innovation, creativity, and time. It has been a rewarding experience and a pleasure to collaborate with each of them. We sincerely thank Frank Pipers and Merial Limited for a grant which made possible the reproduction of color plates for this textbook, and acknowledge their support for the International Cardiac Health Council. We have enjoyed working with our students, interns and residents, technicians, and colleagues, who will continue to be our partners in learning. And to the many pets whom I have treated and from whom I have learned, I remain grateful.

I am especially appreciative of David Sisson and Sydney Moïse who have remained my dear friends through the trials and tribulations of editing this textbook. Together, we ardently sought to capture the current knowledge, collective excitement, and magic that is the hallmark of this rapidly moving field. It is our wish that you will use this textbook with expertise and confidence to improve care for your patients, to stimulate future diagnostic and therapeutic advancements, and to educate trainees who wish to learn cardiology.

PHILIP R. FOX, D.V.M.
The Animal Medical Center
New York, New York
1999

Philip Fox　　Sydney Moïse　　David Sisson

NOTICE

Companion animal practice is an ever-changing field. Standard safety precautions must be followed, but as new research and clinical experience grow, changes in treatment and drug therapy become necessary or appropriate. The authors and editors of this work have carefully checked the generic and trade drug names and verified drug dosages to assure that dosage information is precise and in accord with standards accepted at the time of publication. Readers are advised, however, to check the product information currently provided by the manufacturer of each drug to be administered to be certain that changes have not been made in the recommended dose or in the contraindications for administration. This is of particular importance in regard to new or infrequently used drugs. Recommended dosages for animals are sometimes based on adjustments in the dosage that would be suitable for humans. Some of the drugs mentioned here have been given experimentally by the authors. Others have been used in dosages greater than those recommended by the manufacturer. In these kinds of cases, the authors have reported on their own considerable experience. It is the responsibility of those administering a drug, relying on their professional skill and expericence, to determine the dosages, the best treatment for the patient, and whether the benefits of giving a drug justify the attendant risk. The editors cannot be responsible for misuse or misapplication of the material in this work.

THE PUBLISHER

Contents

I
The Normal Heart: Cardiovascular Structure, Function, and Physiology 1

1. Embryologic Development: The Heart and Great Vessels 3
SANFORD P. BISHOP

2. Cardiovascular Anatomy 13
PHILIP R. FOX, N. SYDNEY MOÏSE, HOWARD E. EVANS, and SANFORD P. BISHOP

3. Normal Cardiovascular Physiology 25
ROBERT L. HAMLIN

II
Examination of the Patient with Cardiovascular Disease 39

4. The History 41
PHILIP R. FOX

5. The Physical Examination 46
DAVID SISSON and STEPHEN J. ETTINGER

III
Diagnostic Methods 65

6. Electrocardiography 67
MICHAEL S. MILLER, LARRY P. TILLEY, FRANCIS W. K. SMITH, JR., and PHILIP R. FOX

7. Radiology 107
PETER F. LORD and PETER F. SUTER

8. Echocardiography and Doppler Imaging 130
N. SYDNEY MOÏSE and PHILIP R. FOX

9. Cardiac Catheterization and Angiocardiography 173
WILLIAM P. THOMAS and DAVID SISSON

10. Nuclear Imaging, Computed Tomography, and Magnetic Resonance Imaging of the Heart 193
GREGORY B. DANIEL and JANICE M. BRIGHT

IV
Abnormal Cardiovascular Function and Principles of Therapy 203

11. Pathophysiology of the Failing Heart 205
ROBERT L. HAMLIN

12. Management of Heart Failure: Principles of Treatment, Therapeutic Strategies, and Pharmacology 216
DAVID SISSON and MARK D. KITTLESON

13. Pulmonary Edema 251
WENDY A. WARE and JOHN D. BONAGURA

14. Pathophysiology and Monitoring of Shock 265
WILLIAM C. SHOEMAKER

15. Treatment of Shock 272
STEVEN C. HASKINS

16. Electrophysiologic Mechanisms for Arrhythmias 291
KENNETH H. DANGMAN

17. Pharmacology and Pharmacokinetics of Antiarrhythmic Drugs 307
WILLIAM W. MUIR, III, RICHARD A. SAMS, and N. SYDNEY MOÏSE

18. Diagnosis and Management of Canine Arrhythmias 331
N. SYDNEY MOÏSE

19. Diagnosis and Management of Feline Arrhythmias 386
PHILIP R. FOX and NEIL K. HARPSTER

20. Pacemaker Therapy 400
N. SYDNEY MOÏSE

21. Cardiopulmonary and Cerebral Resuscitation 427
DENNIS T. CROWE, Jr., PHILIP R. FOX, JENNIFER J. DEVEY, and DAVID SPRENG

22. Syncope and Episodic Weakness 446
JOHN E. RUSH

V
Diseases of the Heart and Circulation 455

23. Prevalence of Cardiovascular Disorders 457
JAMES W. BUCHANAN

24. Congenital Heart Disease 471
JOHN D. BONAGURA and LINDA B. LEHMKUHL

25. Acquired Valvular Heart Disease in Dogs and Cats 536
DAVID SISSON, CLARENCE KVART, and PETER G. G. DARKE

26. Infectious Endocarditis 567
MATTHEW W. MILLER and DAVID SISSON

27. Myocardial Diseases of Dogs 581
DAVID SISSON, MICHAEL R. O'GRADY, and CLAY A. CALVERT

28. Feline Cardiomyopathies 621
PHILIP R. FOX

29. Pericardial Disease and Cardiac Tumors 679
DAVID SISSON and WILLIAM P. THOMAS

30. Canine Heartworm Disease 702
CLAY A. CALVERT, CLARENCE A. RAWLINGS, and JOHN W. McCALL

31. Feline Heartworm Disease 727
RAY DILLON

VI
Effects of Systemic and Metabolic Disorders on the Heart 737

32. Nutrition and Management of Cardiovascular Disease 739
PAUL D. PION, BRUCE W. KEENE, MATTHEW MILLER, and PHILIP R. FOX

33. Cardiac Manifestations of Systemic and Metabolic Disease 757
CLARKE E. ATKINS

34. Hyperthyroidism and Other High Output States 781
PHILIP R. FOX, JOHN D. BROUSSARD, and MARK E. PETERSON

35. Systemic Hypertension: Recognition and Treatment 795
MERYL P. LITTMAN and PHILIP R. FOX

VII
Cardiovascular Pathology 815

36. Cardiovascular Pathology 817
SI-KWANG LIU and PHILIP R. FOX

37. Necropsy Techniques for the Heart and Great Vessels 845
SANFORD P. BISHOP

VIII
Cardiovascular Surgery and Procedure 851

38. Anesthesia and the Heart 853
DIANE E. MASON and JOHN A. E. HUBBELL

39. Basic Cardiovascular Surgery and Procedures 866
GEORGE E. EYSTER

Appendix 883

Index 919

PLATE 1

Eight-month-old, polycythemic cat with cyanotic congenital heart disease (tetralogy of Fallot). Mucous membranes reveal cyanosis (courtesy of Dr. Philip Fox).

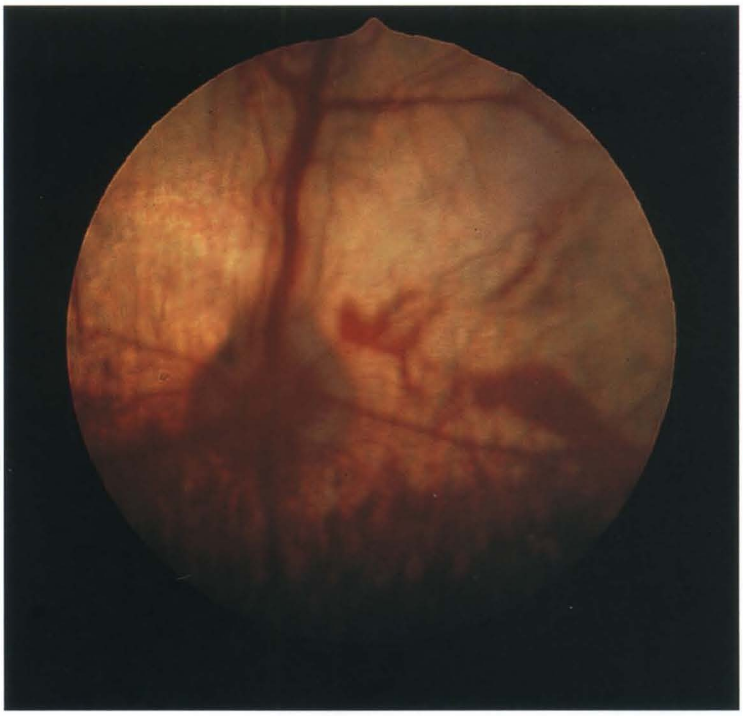


PLATE 2

Retinal photograph from a dog with systemic hypertension. Lesions include preretinal and intraretinal hemorrhage, mild vascular tortuosity, and intraretinal edema (courtesy of Dr. Sandra Van der Woerdt).

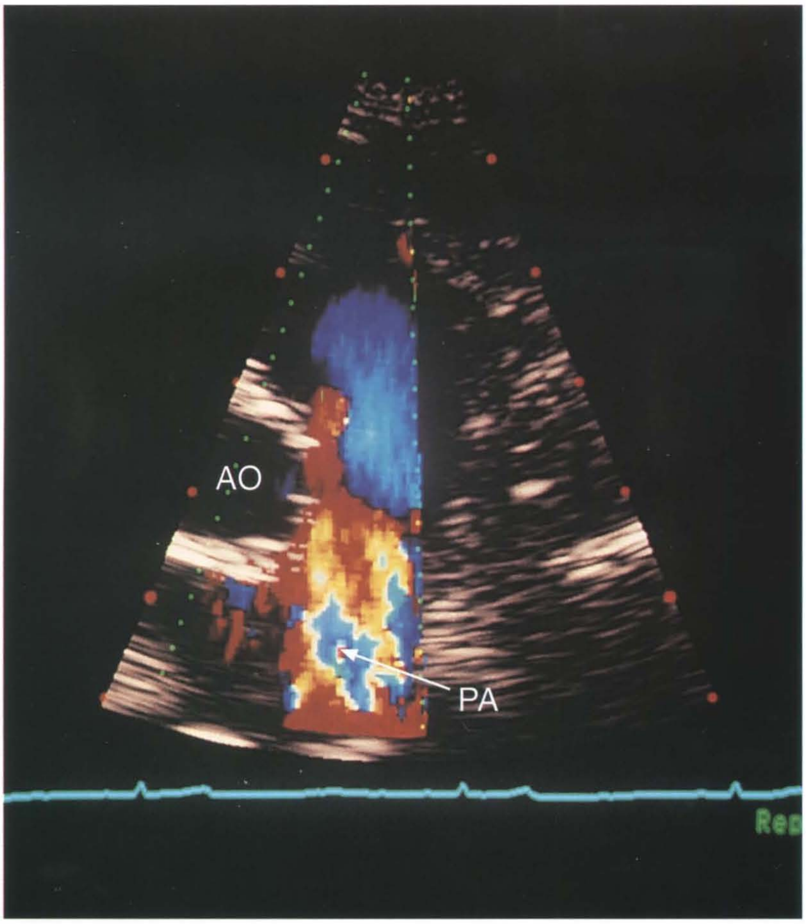


PLATE 3

Color-flow Doppler echocardiogram (short-axis view) recorded at the heart base from a dog with severe pulmonic stenosis. Disturbed systolic flow is recorded as color variance (yellow/red/green) beginning at the pulmonic valve. AO, aorta; PA, pulmonary artery (courtesy of Dr. Philip Fox).

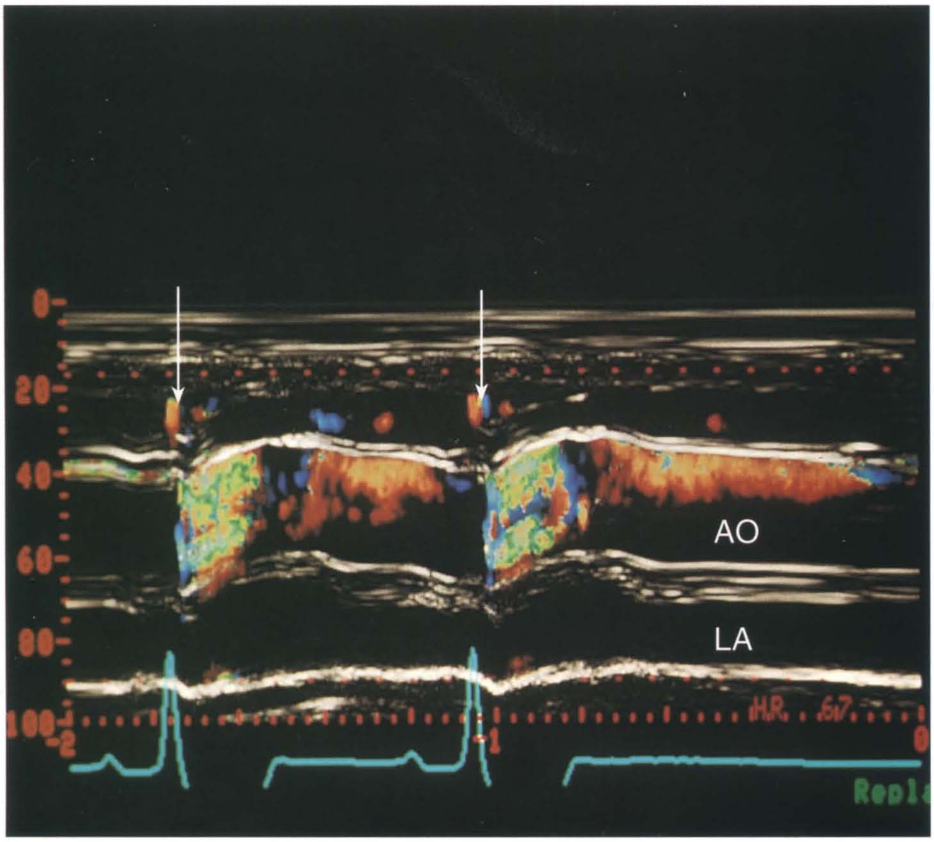


PLATE 4

Color M-mode can be useful to help time flow events. In this dog with subaortic stenosis, highly disturbed, turbulent flow was recorded as color variance (yellow/green) during systolic ejection through the aortic valves. Arrows indicate onset of systole. Pandiastolic aortic regurgitation is coded as red. AO, aortic root; LA, left atrium (courtesy of Dr. Philip Fox).

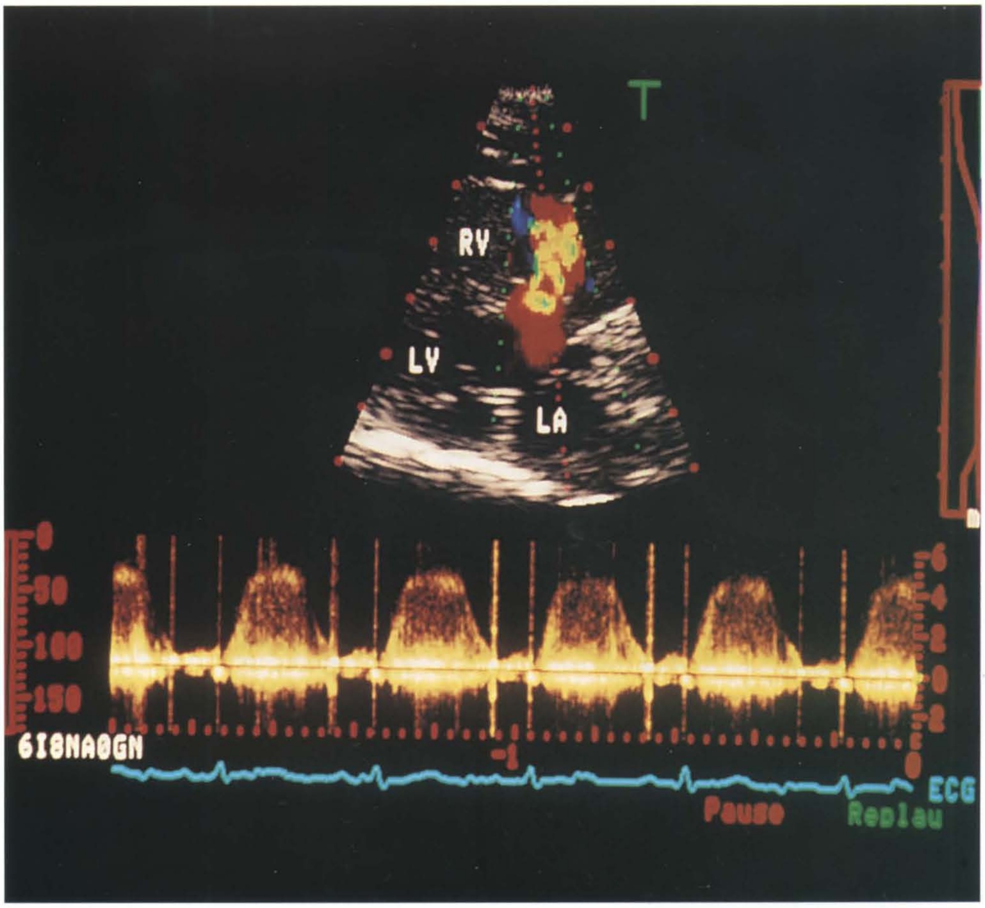


PLATE 5

Top: Color-flow Doppler echocardiogram (right parasternal long-axis view) from a cat with ventricular septal defect (VSD). Blood shunting toward the transducer—from the left ventricle (LV) across the VSD, to the right ventricle (RV)—is coded red. Color variance (yellow/green) results from increased flow velocity. *Bottom:* Transseptal interrogation of the defect by continuous-wave Doppler records a high systolic velocity (5.5 m/sec), suggesting a small ("restrictive") VSD. A maximal gradient of 121 mmHg (i.e., pressure drop across the defect) was estimated using the Bernoulli equation. The spectral trace above the baseline indicates systolic flow toward the transducer (courtesy of Dr. Philip Fox).

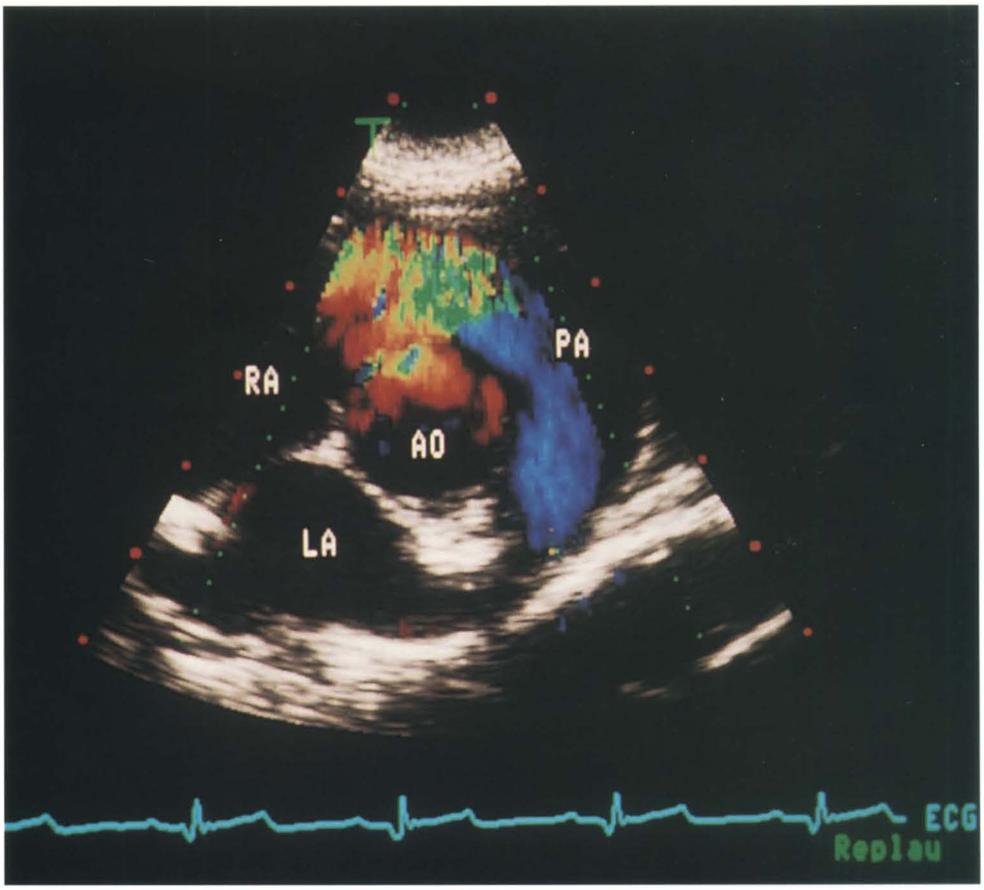


PLATE 6

Color-flow Doppler echocardiogram (right parasternal short-axis view) recorded at the heart base from a dog with a restrictive VSD. Systolic flow crosses the defect below the aortic root (AO), moves anteriorly and toward the RV outflow tract and pulmonary artery (PA). The very bright mosaic of color signals (aliasing) is associated with turbulent flow. Compare the normal, laminar flow through the PA here (coded blue—away from the transducer), with the disturbed flow in Plate 3. LA, left atrium; RA, right atrium (courtesy of Dr. Philip Fox).

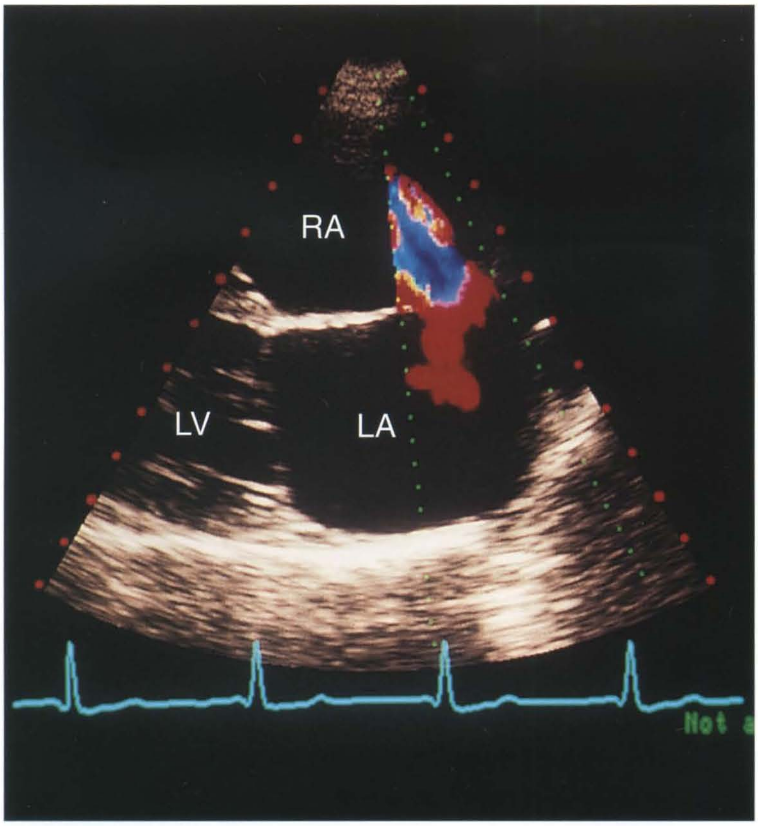


PLATE 7

Color-flow Doppler echocardiogram (right parasternal long-axis view) of a dog with a sinus venosus atrial septal defect. Blood shunts through the defect from the left atrium (LA) into the right atrium (RA) and is coded red, signifying flow toward the transducer. The color signal changes from red to blue indicating the aliasing point (i.e., the point where the blood velocity exceeds the system's ability to accurately record it.) LV, left ventricle (courtesy of Dr. Philip Fox).

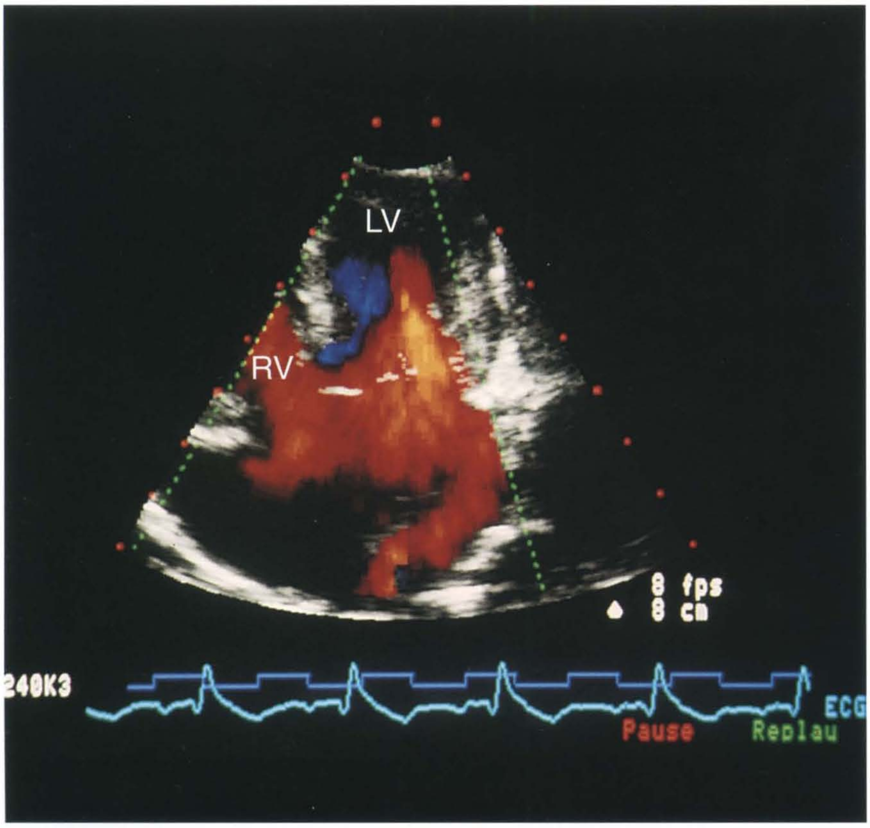


PLATE 8

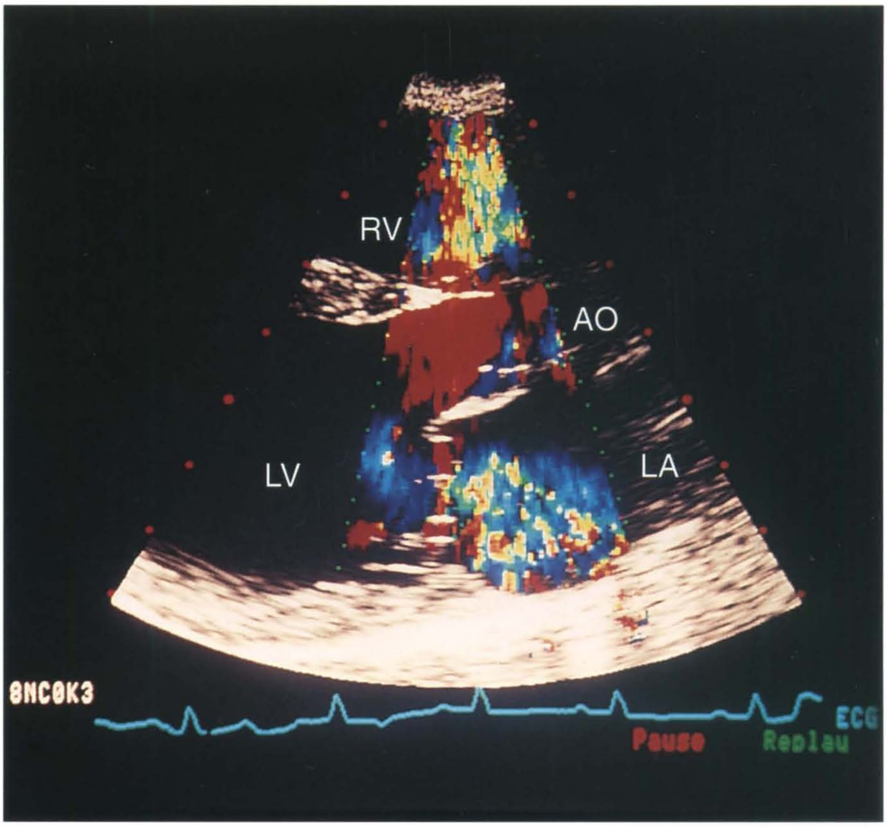
Color-flow Doppler echocardiogram (left apical four-chamber view) of a dog with a large ostium primum atrial septal defect, which comprised part of an endocardial cushion defect. Flow toward the transducer (coded red) crosses the defect in the lower atrial septum, and also moves through the mitral and tricuspid valves to fill each respective ventricle during diastole. LV, left ventricle; RV, right ventricle (courtesy of Dr. Steven Rosenthal).

PLATE 9

Color-flow Doppler echocardiogram (left apical five-chamber view) recorded from the same dog in Plate 8 after surgical repair of the defect. Flow is no longer recorded across the basal atrial septum, but instead travels normally from the LA to the LV during diastolic filling (courtesy of Dr. Steven Rosenthal).

PLATE 10

Color-flow Doppler echocardiogram (right parasternal long-axis view) from a dog with atrioventricular valve endocardiosis and regurgitation. The mitral and tricuspid regurgitant jets are displayed as mosaic colored signals caused by turbulent flow (variance is indicated by yellow/green), originating from the mitral and tricuspid valves, respectively (courtesy of Dr. Philip Fox).



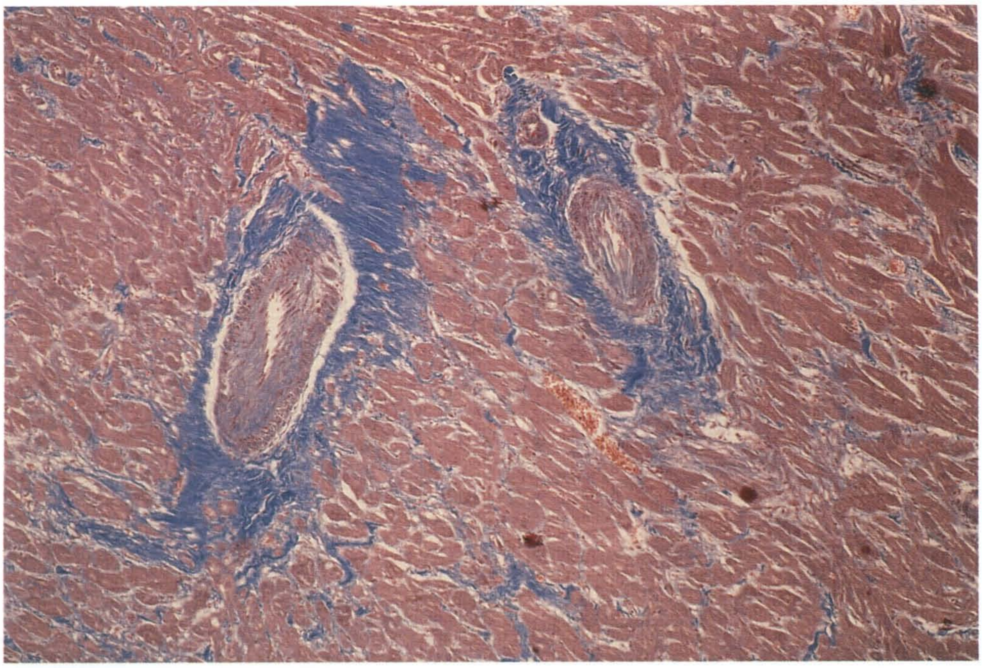


PLATE 11

Photomicrograph (Masson trichrome stain) of a section of ventricular septum from a cat with idiopathic hypertrophic cardiomyopathy. Two abnormal intramural coronary arterioles display severe wall thickening (arteriosclerosis, or "small vessel" disease), and are surrounded by blue staining fibrous connective tissue. Myofiber disarray is present, particularly in the right-hand region (courtesy of Dr. Si-Kwang Liu).

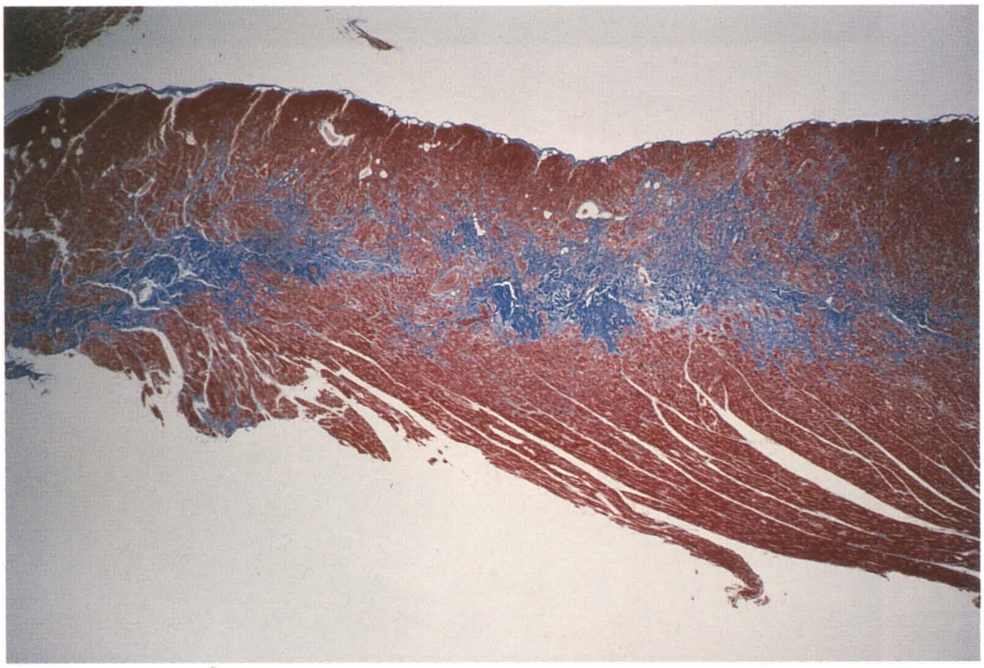


PLATE 12

Photomicrograph (Masson trichrome stain) of a left ventricular myocardial section from a cat with idiopathic myocardial failure. Severe myocardial necrosis is present. Diffuse and massive replacement fibrosis with mid-mural accentuation is indicated by the dark blue staining tissue (courtesy of Dr. Si-Kwang Liu).

I

The Normal Heart: Cardiovascular Structure, Function, and Physiology

1

Embryologic Development: *The Heart and Great Vessels*

SANFORD P. BISHOP

A thorough knowledge of developmental anatomy is essential to assist clinical differentiation of normal and pathologic cardiovascular disorders. Detailed reviews of embryologic development[1–4] and an excellent description of cardiac morphogenesis have been reported.[5]

Developmental abnormalities result in a variety of cardiac defects (chapters 23, 24), the most severe of which cause early embryo death. Only a portion of animals with abnormalities survive to birth with congenital heart disease; many of these result in clinical signs early in life, whereas milder forms may be asymptomatic or not cause signs until adulthood.

EMBRYOLOGY

EARLY FORMATION OF THE HEART

The heart originates as paired structures in the splanchnic mesoderm, first appearing at about the three- to four-somite stage. This mesodermal tissue eventually becomes the myocardium. Shortly afterward, endocardial tissue, also from the mesoderm, combines bilaterally with the myocardial progenitor tissue to form paired endocardial tubes. These paired endocardial tubes migrate centrally and fuse to form a single straight cardiac tube consisting of myocardium, endocardium, and associated extracellular material. At this stage, interference with fusion of the two paired structures can result in formation of two independent beating hearts, one on each side of the embryonic midline.

Conotruncal cardiac malformations result from abnormalities in development of neural crest–derived tissue.[6–9] They include tetralogy of Fallot, transposition of the great vessels, subaortic ventricular septal defects, double outlet right ventricle, and other outflow tract abnormalities.

CARDIAC LOOP

The straight cardiac tube is contained in the primitive pericardial cavity and has the ventral aorta on its anterior end and the omphalomesenteric

veins at the posterior end. The tube undergoes a series of bends and folds to form the cardiac loop with the various clearly defined structures, the sinus venosus, atrium, ventricle, and bulbus cordis (Fig. 1–1). The caudally located sinus venosus receives blood from the entire embryo and is separated from the atrium by the sinoatrial sulcus, the site of the future sinoatrial node or pacemaker of the heart. During final stages of cardiac loop development, the atrium forms two lateral lobes but is still a single chamber. Caudal to the atrium, the ventricle takes on a saccular shape and is separated from the atrium by a distinct atrioventricular canal. The bulbus cordis is separated from the ventricle by the bulboventricular sulcus. The region adjacent to the ventricle will become the infundibular region of the adult heart, and the most cranial portions will form the aorta and pulmonary artery (Fig. 1–2).

VENTRICLE FORMATION

Cardiac contractile activity begins during the early cardiac loop stage when myocytes have discernible actin and myosin contractile proteins.[10, 11] Although valves are not yet formed, forward flow of blood is maintained by constriction of the tube at the atrioventricular canal. The endocardium is separated from the myocardium by an extensive extracellular matrix of glycosaminoglycans and glycoproteins, the *cardiac jelly.* The cardiac jelly aids in forming a valvelike action of the primitive heart, and once pulsatile forward flow of blood is established during cardiac loop formation, blood pressure of about 1 mmHg may be recorded in the chick embryo.[12, 13] By completion of septation at 6 days in the chick embryo, left ventricular systolic pressure is 3.5 mmHg[14] and by the time of hatching, blood pressure is reported to reach 30 mmHg.[15]

During formation of the cardiac loop, the endocardium invaginates through the cardiac jelly and into the myocardium, forming trabeculae that persist into adult life and form the papillary muscles. The cardiac jelly disappears from the ventricular portion with the development of trabeculation but persists longer in the atrioventricular canal and bulbus cordis regions. The cardiac jelly is invaded by endocardial cells and in these latter regions forms the endocardial cushions that participate in cardiac septation.

SEPTATION

After the development of the cardiac loop stage, the heart undergoes a series of septations that divide the left and right sides of the structure. However, openings remain between all chambers, resulting in two parallel communicating circulations. The bulbus cordis elongates and separates into two channels, forming the aorta and pulmonary artery. Muscle tissue disappears distal to the tricuspid valve primordia. The proximal portions of the bulbus cordis form the infundibular muscular regions of the ventricles. The sinus venosus becomes separated from the left atrium by deepening of the atrioventricular sulcus and opens only into the right atrium. The caval veins obtain independent openings into the right atrium, and part of the sinus venosus becomes the coronary sinus (Fig. 1–3*A*). At the same time, the pulmonary veins connect with the left atrium. In the adult heart, the smooth portions of the left and right atrium are derived from the sinus venosus region of the cardiac loop. Irregular pectinate portions are derived from embryonic atria.

In the ventricle, septation begins from the apex by extension of the trabeculation process and growth of tissue toward the atrioventricular canal, forming the

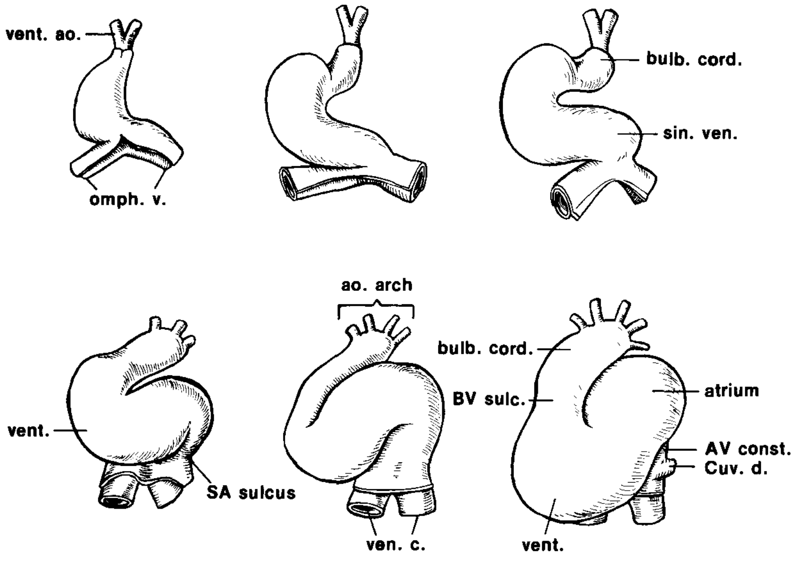


FIGURE 1–1

Ventral views of the developing heart, illustrating formation of the cardiac loop from the straight cardiac tube. ao. arch, aortic arches; AV const., atrioventricular constriction; bulb. cord., bulbus cordis; BV sulc., bulboventricular sulcus; Cuv. d., Cuvier's duct; omph. v., omphalomesenteric veins; SA sulcus, sinoatrial sulcus; sin. ven., sinus venosus; ven. c., venae cavae; vent., ventricle; vent. ao., ventral aortic roots.

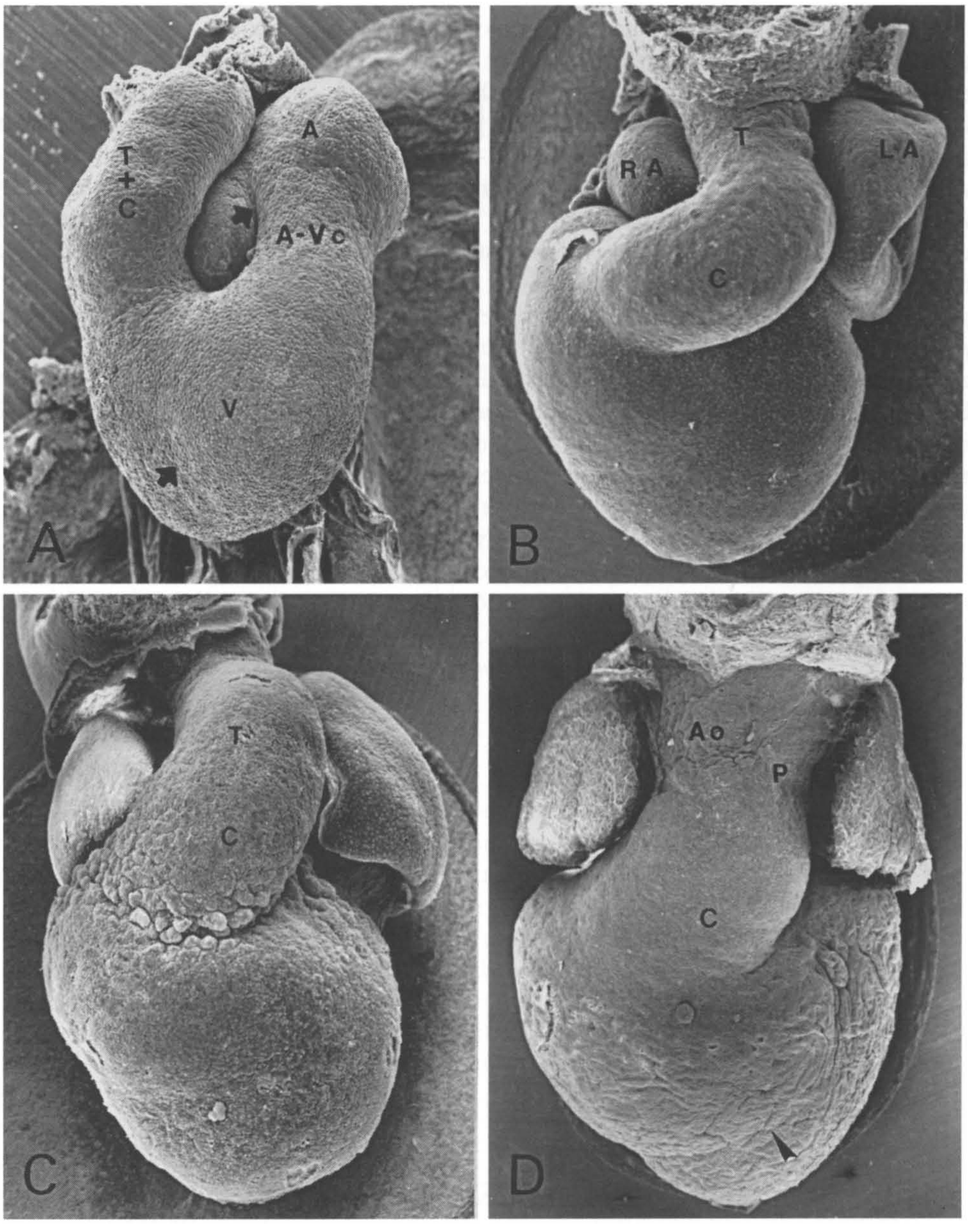


FIGURE 1–2

Scanning electron micrographs of chick embryo hearts, showing modifications of the external form of the heart at postlooping stages (ventral views). (A) Third day of incubation. At this stage, the bulbus cordis *(T + C)* cannot be separated into its two components. Arrows indicate the interatrial *(top)* and interventricular *(bottom)* sulci. (B) Fourth day of incubation. The bulbus is growing longitudinally and bends around a transverse axis. This is the point at which its two components, truncus and conus, can be distinguished. Compare the size of the two atria. (C) Fifth day of incubation. Note the rapid growth of the right atrium. (D) Sixth day of incubation. The proximal segments of the aorta and pulmonary artery are already formed. However, there is no external separation. Note the location of the interventricular sulcus *(arrowhead)*. The apex of the heart is already formed by the left ventricle.
A, atrium; Ao, aorta; A-Vc, atrioventricular canal; C, conus; LA, left atrium; P, pulmonary artery; RA, right atrium; T, truncus; V, ventricle.
(Reproduced by permission from Icardo JM: The growing heart: An anatomical perspective. *In* Zak R (ed): Growth of the Heart in Health and Disease. New York, Raven Press, 1984, p 41.)

primary interventricular foramen (Fig. 1–3*B*). The primary interventricular foramen partially closes by forming a connective tissue mass when the ventral septal tissue fuses with the septal portion of the atrioventricular (AV) cushion. However, the ventral portion of the primary interventricular foramen remains open, becoming the connection of the aorta with the left ventricle. Ventricular septal defects result when this ventricular septal partition fails to close; they may be located anywhere from the pulmonic infundibular region to the aortic outflow region.

In the atrium, the septum primum extends from the dorsal atrial wall toward the atrioventricular canal, forming the ostium primum. This opening is normally completely occluded when the septum primum fuses with the dorsal and ventral endocardial cushions (Fig. 1–3*C*). At the same time, perforations appear in the superior portion of the septum primum and eventually coalesce, forming the ostium secundum. Another septum—the septum secundum—arises from the dorsal atrial wall, descends down over the right side of the septum primum, and joins the atrioventricular canal cushion. An opening called the fossa ovalis persists in the septum secundum. This fossa ovalis is normally covered by the septum primum, forming the valve of the fossa ovalis (Fig. 1–3*D*). Defects in this region include (1) patient foramen ovale (due to failure of normal postnatal anatomic closure of this opening), (2) ostium primum defects (due to incomplete fusion of the septum primum with the atrioventricular cushions), and (3) ostium secundum defects (the septum primum opening remains unduly large and the septum primum does not cover the fossa ovalis).

Atrioventricular valve formation occurs late in the

first trimester in mammals, long after the cardiac septation is completed.[16] The atrioventricular canal forms the dorsal and ventral endocardial cushions, which fuse with the atrial and ventricular septa, giving rise to the mitral and tricuspid valves (Figs. 1–3*C,D*). The valves form from tissue folds derived in ventricular walls and endocardial cushions, through a process of mesenchymal cell death and mesenchymal transformation of endocardial cells. Perforations in the cusp appear and coalesce to form the chordae tendineae and papillary muscles.[17] Developmental anomalies in the atrioventricular cushions result in persistent openings between the chambers, usually accompanied by clefts in the anterior leaflet of the mitral valve, and sometimes in the tricuspid valve as well. These endocardial cushion defects are especially common in the cat.

Semilunar valves also develop relatively late in cardiac morphogenesis. Following conotruncal septation, three cushions form within the aortic and pulmonary lumens, consisting of cardiac jelly seeded with mesenchymal cells and covered with endothelium. Abnormal blood flow during development results in thickened leaflets and commissural fusion.[18, 19] A range of pulmonic valve abnormalities have been described in the beagle dog related to a recessive gene with incomplete penetrance.[20] Additional conotruncal lesions, including tetralogy of Fallot, have been described in the dog attributable to a genetic basis.[21, 22] Pathogenesis of other defects involving the semilunar valves and subvalvular outflow tract region may be due to a genetic predisposition in combination with abnormal flow characteristics during valve formation.

AORTIC ARCHES

Six pairs of aortic arches develop with the embryonic heart. In mammals, the first, second, and fifth pairs

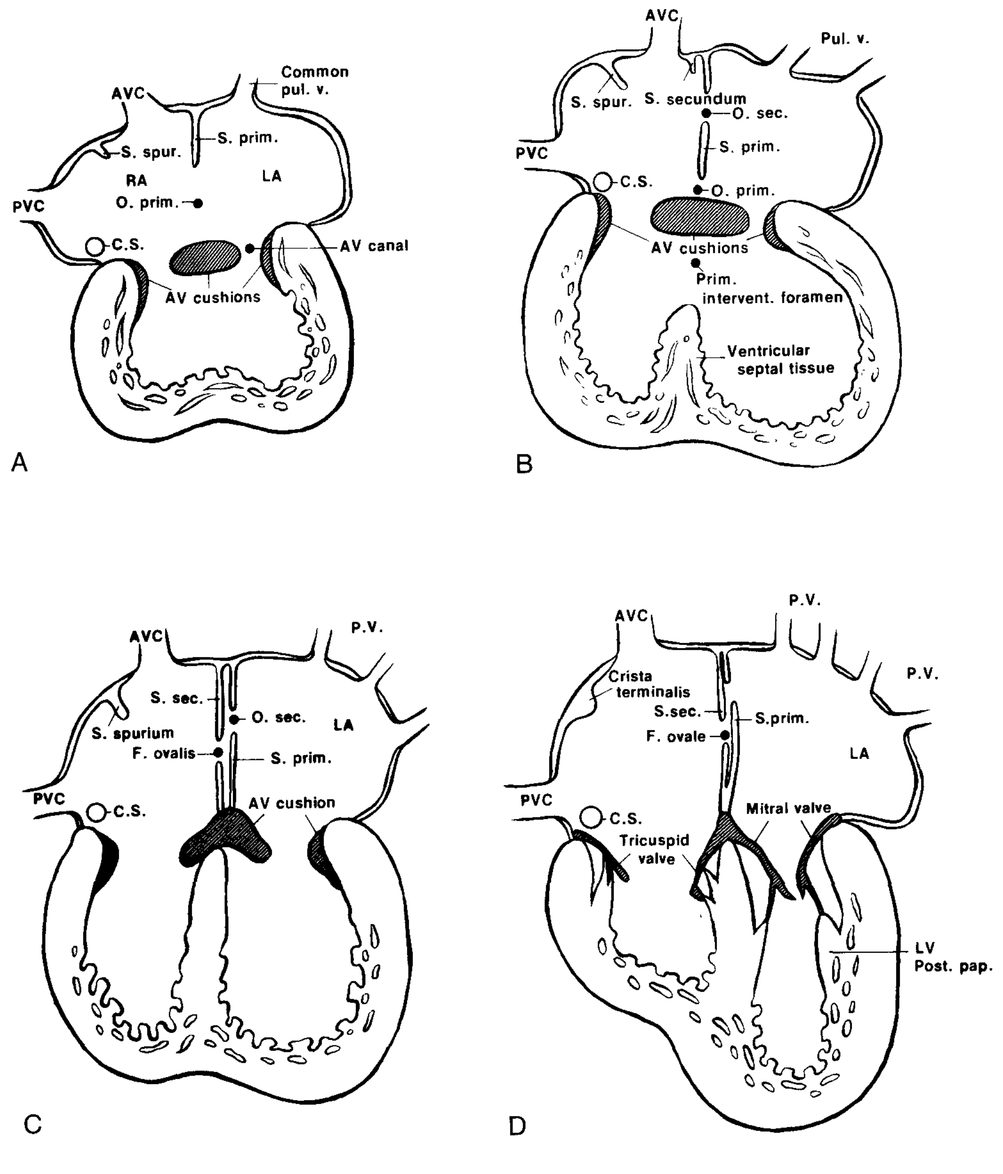


FIGURE 1–3

Septal development of the heart. (A–D) Drawings illustrating development of ventricular and atrial septa and formation of atrioventricular valves by the AV endocardial cushions (from the postloop stage to late fetal development). AVC, anterior vena cava; C.S., coronary sinus; F. ovalis, fossa ovalis; F. ovale, foramen ovale; LA, left atrium; LV Post. Pap., left ventricle posterior papillary muscle; O. sec., ostium secundum; O. prim., ostium primum; Pul. v., P.V., pulmonary veins; PVC, posterior vena cava; RA, right atrium; S. sec., septum secundum; S. prim., septum primum; S. spurium, S. spur., septum spurium.

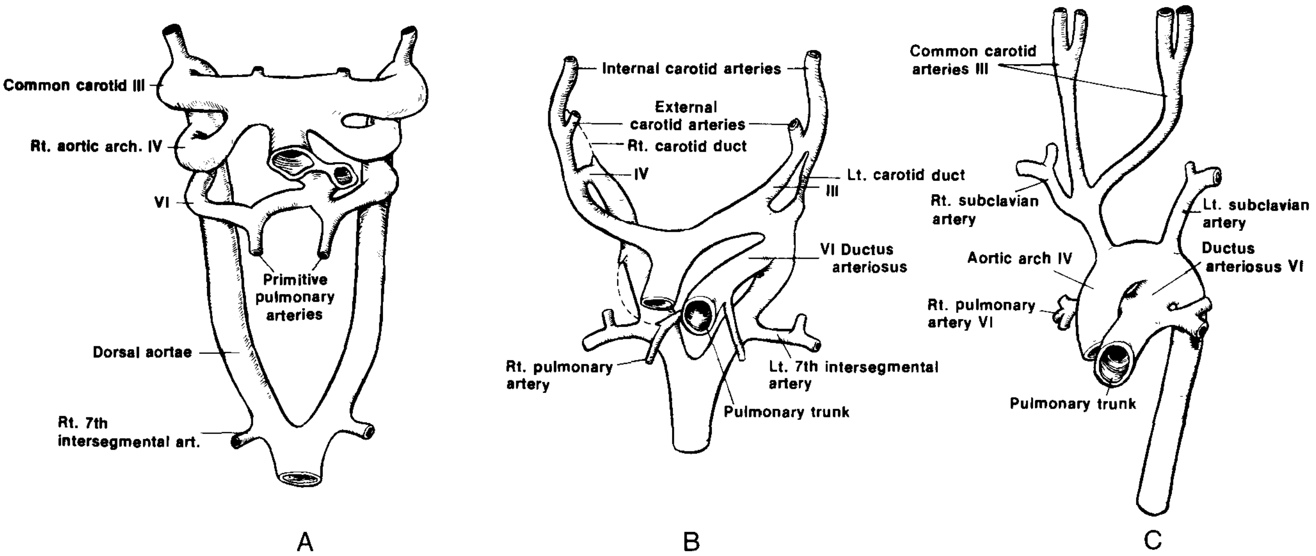


FIGURE 1-4

(A–C) Development of the aortic arch system in the dog and cat. Only the third, fourth, and sixth arches are retained, and the seventh intersegmental arteries form the subclavian arteries. (Modified from Van Mierop LHS, Kutsche LM: Embryology of the heart. *In* Hurst JW (ed): The Heart. Vol 1, 5th ed. New York, McGraw-Hill, 1982, p 7.)

regress completely at an early stage, and the third pair forms the internal carotid arteries. The left fourth arch forms a portion of the aortic root, joining with the persistent left dorsal aorta. The right fourth arch forms the root of the subclavian artery, and the distal right dorsal aorta disappears. The sixth arches form the pulmonary arteries, and the distal portion of the left retains its connection with the dorsal aorta as the ductus arteriosus (Fig. 1–4; see also Fig. 24–39).

A variety of vascular ring anomalies are possible due to malformations in the development of the aortic arches. The most common in dogs is persistence of the right fourth aortic arch. This results in entrapment of the esophagus between the pulmonary artery, trachea, and the ligamentum, or patent ductus arteriosus.

PULMONARY VEINS

The lungs develop from primitive foregut independent of the heart. They drain during early embryogenesis to the cardinal and umbilicovitelline veins. Pulmonary veins develop from the left atrium to communicate with pulmonary venous drainage. Failure of this system to develop normally can result in anomalous pulmonary venous drainage.

CORONARY VASCULATURE

The coronary circulation appears relatively late in development, showing up initially as remnants of the trabecular channels remaining patent to form the initial capillary bed. Prior to this time, myocardial nutrition is supplied by the trabecular myocardial sinusoidal system. Coronary arteries arise as buds from the aortic root that connects to the capillaries. Although mechanisms of coronary vascular development are unknown, a variety of physical and chemical factors have been experimentally shown to influence vascular growth.[23] These signals include mechanical factors, endothelial migration, chemical signals from perivascular cells, and autonomic nerve fibers, which extend into the myocardium at the same time as the coronary vessels develop.

SPECIALIZED CONDUCTION TISSUE

Functional specialized conduction tissue may first be recognized at the end of the cardiac loop stage,[24–27] when the heart has already been beating for some time. The specialized conducting tissue, including the sinus and atrioventricular nodes, and the Purkinje fibers appear to develop from myocardial cells, forming rings that fuse at the crux of the heart.[28] Cells in the sinus venosus beat at a faster rate than those of the ventricle, even in the cardiac loop stage. Although little is known about the ontogeny of the conducting system, these more rapidly beating cells in the sinus venosus presumably become the sinus node.[29]

TRANSITION FROM FETAL TO NEONATAL BLOOD FLOW

During circulatory development from the embryonic to fetal to neonatal stage, transformation occurs

in blood flow, from a single circular system to a double parallel circuit and finally, to a double circulation in series (Fig. 1–5). In the early embryo, all blood enters the heart through a single venous sinus, traverses straight through the heart, and is distributed to the body and placenta by way of the conotruncal bulb and the aortic arches. As partitioning develops, a double circuit is formed with parallel flow and cross-over proximal and distal to the ventricles. Virtually all blood entering the right atrium from the head and forepart of the body is shunted by a muscular fold on the atrial septum adjacent to the fossa ovalis directly into the right ventricular cavity. This poorly oxygenated blood is pumped by the right ventricle to the pulmonary artery, across the ductus arteriosus, to the descending thoracic aorta *en route* to the placenta and lower body. The pulmonary vasculature has very high resistance owing to fluid surrounding the vessels and owing to vasoconstriction in response to the low blood oxygen content. Only 5 to 10 percent of right ventricular and pulmonary artery blood traverses the lungs.

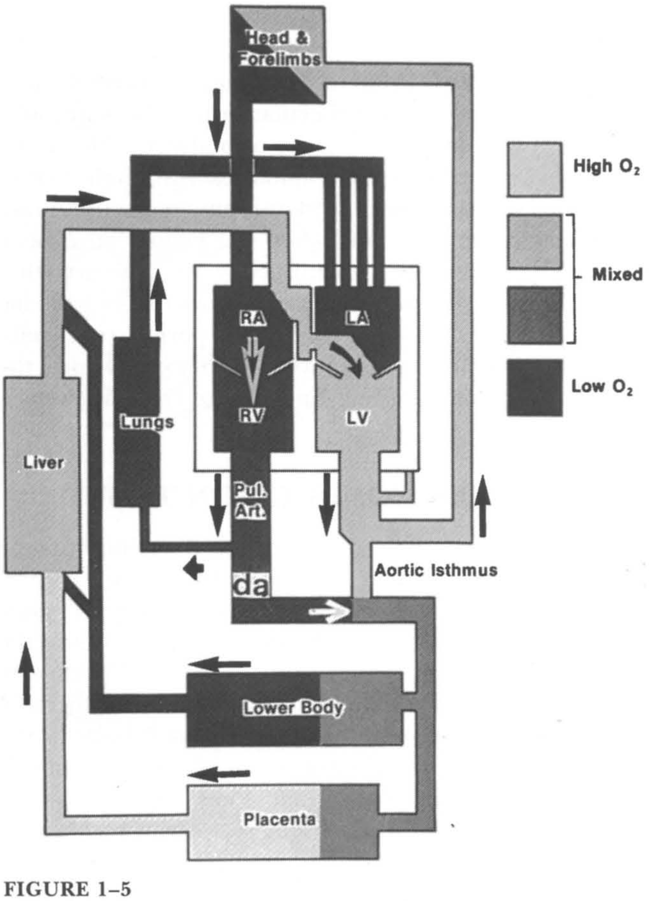


FIGURE 1–5

Diagrammatic representation of blood circulation during the late fetal period. Note that the most highly oxygenated blood returning to the heart from the placenta via the posterior vena cava is shunted mainly across the interatrial septum to the left ventricle, and that vessels to the heart and head receive this highly oxygenated blood. Oxygen-depleted blood coming from the head is returned to the right ventricle, traverses the ductus arteriosus, and enters the aorta distal to the vessels to the heart and head *(white arrow)*. da, ductus arteriosus.

Highly oxygenated blood returning from the placenta and umbilical vein crosses the ductus venosus and enters the right atrium through the postcava. The anatomic relationship of the postcava and the fossa ovalis allows most of this blood to be shunted directly through the fossa ovalis to the left atrium and ventricle. This highly oxygenated blood then enters the root of the aorta where most is distributed to the head and heart. The remainder traverses the aortic isthmus to be mixed with poorly oxygenated blood entering the aorta through the ductus arteriosus. The oxygen-poor blood from the distal postcava is preferentially shunted to the tricuspid valve and enters the right ventricle.[30] Thus, two parallel circuits are present in the fetal period, which deliver highly oxygenated blood to the brain and heart and less well oxygenated blood to the placenta.

Abnormalities of cardiac development do not cause functional abnormality in the fetus as long as there is communication between the right and left sides of the circulatory system. However, stenoses and abnormal circulatory patterns may result in reduced flow, causing underdevelopment or hypoplasia of the affected chamber or vessel. Semilunar valve stenoses (e.g., pulmonic stenosis) may cause chamber enlargement proximal to the stenosis due to increased right ventricular workload. Experimentally, left ventricular enlargement may be induced by placing a band on the aortic arch in the fetus, or left ventricular hypoplasia may be caused by inflow obstruction to the left ventricle.[31] Right ventricular enlargement has been produced in fetal lambs by pulmonary artery constriction.[32]

BLOOD FLOW CHANGES AT BIRTH

At the time of birth and during the subsequent early neonatal period, circulatory changes result in the formation of two separate circuits in series. When air is introduced into the lungs, the fluid media surrounding the vasculature is replaced, thus reducing vascular resistance. With exposure to oxygen, pulmonary vasculature dilates. At the same time, the placental circulation is removed. This increases systemic resistance and prevents right-to-left blood flow through the ductus arteriosus. The musculature of the ductus arteriosus is highly sensitive to oxygen and contracts when exposed to the now increased oxygen content of blood coming from the lungs.[33, 34] In addition, the ductus arteriosus musculature is responsive to prostaglandins that are present at birth, and its closure may be induced by prostaglandin inhibition.[35, 36]

In the fetus, approximately two thirds of the returning blood enters the right ventricle, causing the right side of the heart to be as large as or larger than

the left side. With closure of the ductus arteriosus and reduction in pulmonary resistance, a larger volume of blood now enters the left atrium. This increases left atrial pressure and forces the septum primum flap against the septum secundum. Effective functional closure of the fossa ovalis occurs, completing the formation of two circulatory systems in series.

After the completion of septation, the fetus enters a rapid growth phase, and there is a progressive rise in arterial blood pressure. In the sheep, peak systolic pressure at 120 to 130 days of gestation (of 145 days) is reported to be 45 to 50 mmHg.[32, 37] In chick embryos, arterial pressure has been reported to be up to 30 mmHg at hatching.[15] In the newborn rat we have measured femoral artery blood pressure using a servonull micropressure system; at birth, mean femoral artery pressure was 18 mmHg, increasing to 30 mmHg by 3 days of age, 50 mmHg by 12 days, and 75 mmHg by 21 days of age.[38] In the newborn dog we have measured ventricular pressure by transthoracic puncture of the left and right ventricles with a 21-gauge needle. In newborn puppies, systolic pressure was 35 to 50 mmHg in the left ventricle and 23 to 40 mmHg in the right ventricle. Left ventricular pressures rapidly increased to 75 to 90 mmHg at 3 to 7 days of age, and to 120 mmHg by 3 to 4 weeks of age, while right ventricular pressure remained at 20 to 30 mmHg.[38a]

FETAL AND NEONATAL MYOCARDIAL CELL GROWTH

In fetal life, right ventricular blood flow is approximately twice that of the left ventricle. As a result, right ventricular muscle mass equals or exceeds that of the left ventricle until the time of birth. Although very few data are available, pressures in both ventricles *in utero* are presumably nearly equal, since there is large open communication between the two parallel circulatory systems. Following birth, however, left ventricular pressure rapidly increases, while right ventricular pressure remains stable.

NEONATAL VENTRICULAR GROWTH

In the normally growing neonatal dog, right ventricular free wall weight remains stable for approximately 10 days after birth. Left ventricular weight increases continuously in a linear fashion from the time of birth (Fig. 1–6). Right ventricular free wall weight is only slightly less than combined left ventricle plus septum (including the right ventricular portion of the septum) at the time of birth. The relationship rapidly changes,

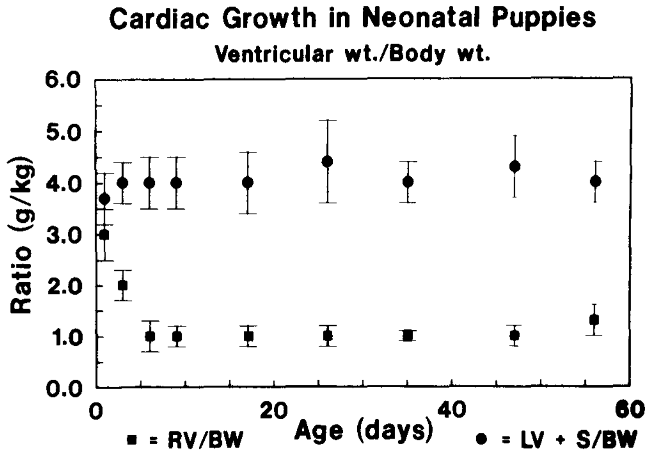


FIGURE 1–6

Graph displaying ratios (g/kg of left ventricle plus septum to body weight [BW], and right ventricular free wall to BW) in normally growing neonatal dogs. Values are expressed as mean ± SD for 66 dogs (3 to 17 dogs per sampled time period). LV, left ventricle; S, septum; RV, right ventricle.

and by 2 weeks of age, the adult ratio of right-to-left ventricular weight is obtained. Thereafter, growth is proportionate between left and right ventricles.

CONVERSION FROM HYPERPLASTIC TO HYPERTROPHIC MYOCYTE GROWTH

During the embryonic and fetal growth periods, increase in heart mass is predominantly a result of cell number multiplication (i.e., *hyperplasia*). Cellular hyperplasia continues into the early neonatal period, when the cells enter a transitional stage of mixed hyperplastic and hypertrophic growth. Finally, the myocytes undergo a final nuclear mitosis, often without a subsequent cellular division, resulting in many binucleated cells.[39] In the dog, this transition period starts at about 2 weeks of age,[40] and by 6 weeks of age, 80 to 85 percent of canine myocytes are binucleated.[40, 41] Thereafter, virtually all increase in cardiac mass is due to increase in myocyte size (i.e., *hypertrophy*), with addition of other cellular components such as coronary vasculature and connective tissue.

EFFECT OF WORK OVERLOAD ON THE FETAL AND NEONATAL HEART

The type of myocardial cell growth resulting from a pressure or volume overload will determine the cellular response. For example, severe pulmonic stenosis will produce a load on both ventricles during the fetal

period, causing biventricular enlargement due to an increased number of myocytes (hyperplasia). Both ventricles are involved since there is free communication between cardiac chambers in the fetus. The massive cardiac enlargement at birth will be due to increased numbers of normal-sized cells. On the other hand, canine congenital subaortic stenosis does not typically result in severe outflow tract obstruction until the animal is several months of age. The mechanism of cell growth at this age is hypertrophy, and compensatory myocardial thickening will be the result of increased cell size with no increase in cell number. Although the clinical significance of these two responses to increased work overload has received little study, the different mechanisms of cellular response could result in different outcomes to surgical or therapeutic treatment.

MYOCARDIAL ULTRASTRUCTURE

During embryonic and early fetal development, cardiac myocytes are poorly differentiated, with randomly arranged myofilaments. Cells have a spherical or ovoid shape, and intercellular connections are not developed. By the time of birth, myocytes have become elongated and there is a definite longitudinal orientation of myofilaments and organization into myofibrils. Presumably, this is at least partially a consequence of remodeling effects caused by intraluminal pressure. During the continued postnatal hyperplastic growth phase, intercellular connections are very poorly developed, and there is an immature interstitial collagenous connective tissue. Following completion of the last cellular division and the initiation of hypertrophic growth, the cellular ultrastructure rapidly assumes the adult ultrastructural appearance, and all further growth is due to uniform addition of all cellular components.

In the early neonatal period, myocytes have a tapered shape, and there is an absence of T tubules in canine myocardium. Myocytes have a cross-sectional area of about 30 μm^2, and the myofibrils are located at the cell periphery.[40] Both myofibrils and mitochondria are relatively sparse compared with adult myocardium. Glycogen and ribosomes are abundant. Intercellular junctions are present but do not have the transverse steplike structure present in mature myocardium. Components of the intercalated disc, including desmosomes, filament attachment areas (fascia adherens), and nexus regions, are present around the cell periphery. Mitoses are frequently evident in neonatal cardiac myocytes. During mitosis, there is dissolution of myofibrillar organization with complete loss of Z-band material.

By 6 weeks of age in the dog, virtually all mitotic activity has ceased, and both the few remaining single nucleated cells and double nucleated cells are increasing in size. Intercalated discs are well formed, and individual myocytes have the characteristic features of adult heart muscle cells (Fig. 1–7). T tubules are present, providing an extension of the sarcolemmal surface area that penetrates to the deepest part of each cell. The sarcolemma makes intimate contact with the sarcoplasmic reticulum, both along the outer surface and along the T tubules (Fig. 1–8). These junctional areas

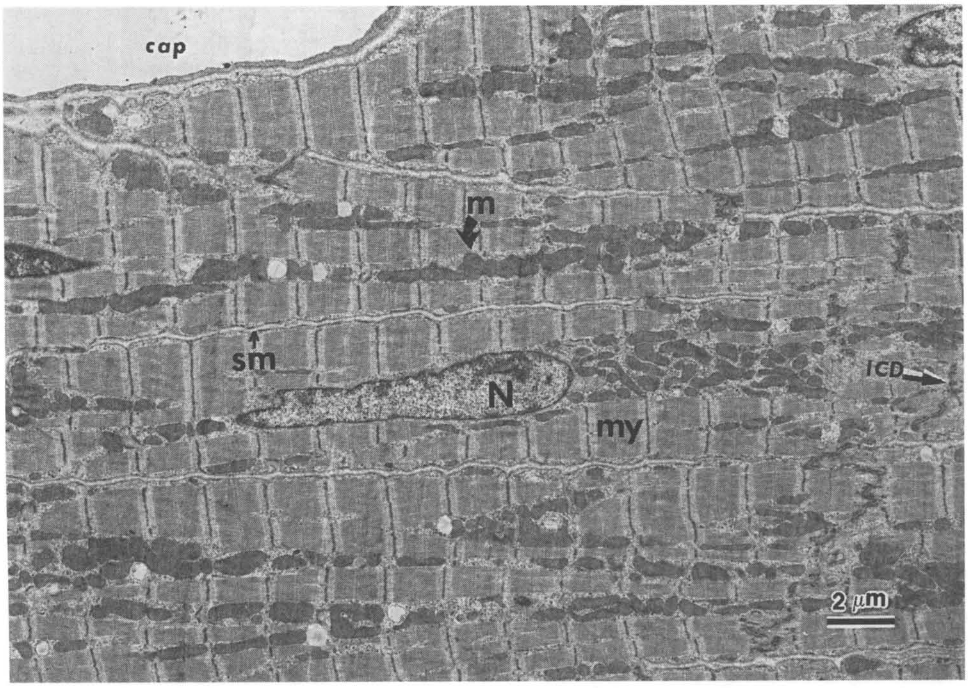


FIGURE 1–7

Electron micrograph of the left ventricular myocardium of a normally growing 8-week-old dog. Although myocyte size has not attained that of the adult, internal cell structure is indistinguishable from that of the adult. Note uniform transverse sarcomere alignment of myofibrils *(my)*, central location of nuclei *(N)*, intercalated discs *(ICD, arrow)*, mitochondria *(m, arrow)*, and distinct sarcolemmal membranes *(sm, arrow)*, with very little interstitial space. Cap, capillary. Bar = 2 μm.

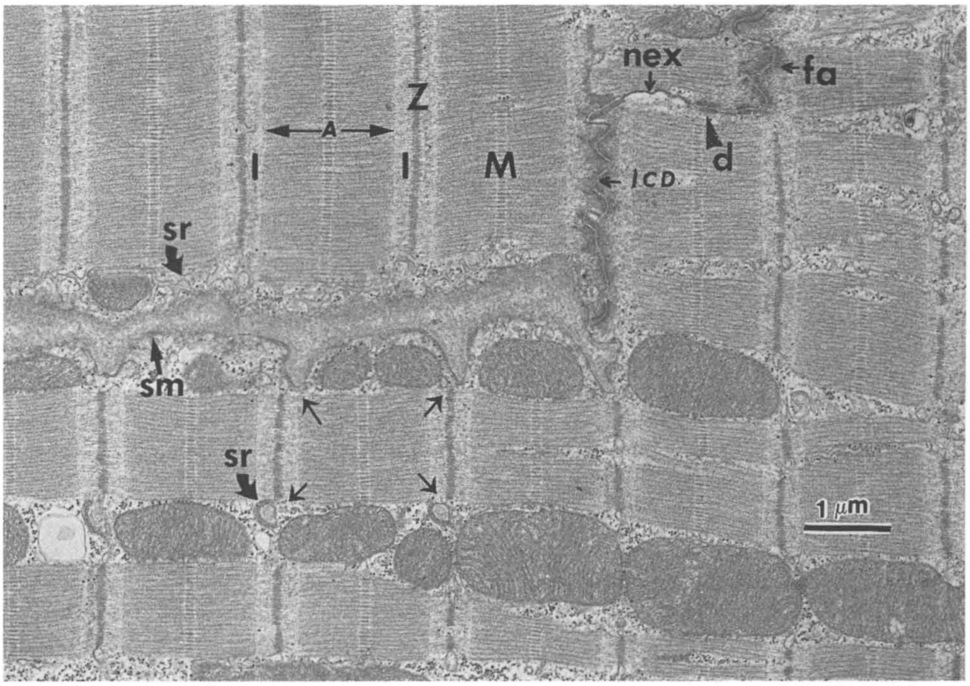


FIGURE 1–8

Electron micrograph of normal adult canine left ventricle at higher magnification than in Figure 1–7. Intercalated discs (ICD) have nexuses or gap junctions *(nex)*, desmosomes *(d)*, and filament attachment areas *(fa)*. The sarcolemma *(sm)* invaginates at the Z-lines *(Z)* to form the T-tubule system *(four arrows)*. The sarcoplasmic reticulum *(sr)* is intimately associated with the sarcolemma and T tubules and surrounds the myofibrils. The sarcomere is composed of myosin-containing A bands *(A)*, central M lines *(M)*, and light I bands *(I)* flanking the Z lines. Bar = 1 μm.

are the site of calcium and other ion transport into the sarcoplasmic reticulum, an important component of excitation contraction coupling. Well-organized myofibrils fill the entire cytoplasm, and mitochondria are diffusely distributed between myofibrils. Nuclei are centrally located, with clusters of mitochondria at their poles.

The contractile apparatus of cardiac muscle consists of an overlapping arrangement of thin actin and thick myosin filaments, together with a variety of other contractile proteins separated into sarcomeres by dense Z-bands (Fig. 1–8). Sarcomeres are aligned in series to form myofibrils, which have branching interconnections and extend the entire length of the cell. Myofibrils are surrounded by an intimate network of sarcoplasmic reticulum, which serves both as a calcium source and a sink during myocyte contraction (chapter 3).

REFERENCES

1. VanMierop LHS, Kutsche LM. Embryology of the heart. *In* Hurst JW (ed): The Heart. New York, McGraw-Hill, 1982, p 7
2. Los JA. Embryology. *In* Watson H (ed): Paediatric Cardiology. St. Louis, CV Mosby, 1968, p 1
3. Boyd JD. Development of the heart. *In* Handbook of Physiology. Vol 3. Washington, DC, American Physiological Society, 1965, p 2511
4. Moorman AFM, Lamers WH. Molecular anatomy of the developing heart. Trends Cardiovasc Med 4:257, 1994
5. Icardo JM. The growing heart: an anatomical perspective. *In* Zak R (ed): Growth of the Heart in Health and Disease. New York, Raven Press, 1984, p 41
6. de la Cruz MV, Gomez CS, Artega NM, Arguello C. Experimental study of the development of the truncus and the conus in the chick embryo. J Anat 123:661, 1977
7. Kirby ML, Gale TF, Stewart DE. Neural crest cells contribute to normal aorticopulmonary septation. Science 220:1059, 1983
8. Kirby ML, Turenage KL, Hays BM. Characterization of conotruncal malformations following ablation of "cardiac" neural crest. Anat Rec 213:87, 1985
9. Clark EB. Mechanisms in the pathogenesis of congenital cardiac malformations. *In* Pierpont MEM, Moller JH (eds): Genetics of Cardiovascular Disease. Boston, Martin Nijhoff Publishing, 1986, p 3
10. Manasek FJ. Embryonic development of the heart. I. A light and electron microscopic study of myocardial development in the early chick embryo. J Morphol 125:329, 1968
11. Lindner E. Myofibrils in the early development of chick embryo hearts as observed with the electron microscope. Anat Rec 136:234, 1960
12. VanMierop LHS, Bertuch J Jr. Development of arterial blood pressure in the chick embryo. Am J Physiol 212:43, 1967
13. Clark EB, Hu N, Dummett JL, et al. Ventricular function and morphology in chick embryo from stages 18 to 29. Am J Physiol 250:H407, 1986
14. Hu N, Clark EB. Hemodynamics of the stage 12 to stage 29 chick embryo. Circ Res 65:1665, 1989
15. Girard H. Arterial pressure in the chick embryo. Am J Physiol 224:454, 1973
16. Pexieder T. Prenatal development of the endocardium: a review. Scan Electron Microsc 2:223, 1981
17. Arrechedera H, Strauss M, Arguello C, et al. Ultrastructural study of the myocardial wall of the atrioventricular canal during the development of the embryonic chick heart. J Mol Cell Cardiol 10:885, 1984
18. Colvee E, Hurle JM. Malformations of the semilunar

valves produced in chick embryos by mechanical interference of cardiogenesis. Anat Embryol 168:59, 1983
19. Atkins DL, Clark EB, Marvin WJ. Foramen ovale/atrial septum ratio: a marker of transatrial blood flow. Circulation 66:28, 1982
20. Patterson DF, Haskins ME. Hereditary dysplasia of the pulmonary valve in beagle dogs. Am J Cardiol 47:631, 1981
21. Patterson DF, Pyle RL, VanMierop L, et al. Hereditary defects of the conotruncal septum in keeshond dogs: pathologic and genetic studies. Am J Cardiol 34:187, 1974
22. Pyle RL, Patterson DF, Chacko S. The genetics and pathology of discrete subaortic stenosis in the Newfoundland dog. Am Heart J 92:324, 1976
23. Ryan TJ, Barnhill RL. Physical factors and angiogenesis. *In* Nugent J, O'Connor M (eds): Development of the Vascular System. London, Pittman Ciba Foundation, 1983, p 80
24. Paff GH, Boucek RJ, Klopfenstein HS. Experimental heart-block in the chick embryo. Anat Rec 149:217, 1964
25. Forsgren S, Thornell LE, Eriksson A. The development of the Purkinje fibre system in the bovine fetal heart. Anat Embryol 159:125, 1980
26. Lieberman M, Pas de Carvalho A. The electrophysiological organization of the embryonic chick heart. J Gen Physiol 49:351, 1965
27. Lieberman M. Initiation of cardiac contractions. *In* Ferrans VJ, Rosenquist GC, Weinstein C (eds): Cardiac Morphogenesis. New York, Elsevier, 1985, p 141
28. Marino TA, Severdoa J. The early development of the AV node and bundle in the ferret heart. Am J Anat 167:299, 1983
29. Sperelakis N: Development changes in membrane electrical properties of the heart. *In* Sperelakis N (ed): Physiology and Pathophysiology of the Heart. Boston, Martin Nijhoff Publishing, 1984, p 543
30. Rudolph AM. Distribution and regulation of blood flow in the fetal and neonatal lamb. Circ Res 57:811, 1985
31. Fishman NH, Hof RB, Rudolph AM, Heymann MA. Models of congenital heart disease in fetal lambs. Circulation 58:354, 1978
32. Pinson CW, Morton MJ, Thornburg KL. Mild pressure loading alters right ventricular function in fetal sheep. Circulation 68:947, 1991
33. Born GVR, Dawes GS, Mott JD, Rennick BR. The constriction of the ductus arteriosus caused by oxygen and by asphyxia in newborn lambs. J Physiol 132:304, 1956
34. Knight DH, Patterson DF, Melbin J. Constriction of the fetal ductus arteriosus induced by oxygen, acetylcholine, and norepinephrine in normal dogs and those genetically predisposed to persistent patency. Circulation 47:127, 1973
35. Coceani F, Olley PM, Bodach E. Lamb ductus arteriosus: effect of prostaglandin synthesis inhibitors on the muscle tone and the response to prostaglandin E_2. Prostaglandins 9:299, 1975
36. Friedman WF, Hirschklau MJ, Printz MP. Pharmacologic closure of patent ductus arteriosus in the premature infant. N Engl J Med 295:526, 1976
37. Hawkins J, Van Hare GF, Schmidt KG, Rudolph AM. Effects of increasing afterload on left ventricular output in fetal lambs. Circ Res 65:127, 1989
38. Clubb FJ Jr, Bell PD, Kriseman JD, Bishop SP. Myocardial cell growth and blood pressure development in neonatal spontaneously hypertensive rats. Lab Invest 56:189, 1987
38a. Bishop SP. Unpublished data, 1995
39. Clubb FJ Jr, Bishop SP. Formation of binucleated myocardial cells in the neonatal rat: an index for growth hypertrophy. Lab Invest 50:571, 1984
40. Bishop SP, Hine P. Cardiac muscle cytoplasmic and nuclear development during canine neonatal growth. *In* Roy P (ed): Recent Advances in Studies on Cardiac Structure and Metabolism. Vol 8. The Cardiac Sarcoplasm. Baltimore, University Park Press, 1975, p 77
41. Vahouny GV, Wei RW, Tamboli A, Albert EN. Adult canine myocytes: isolation, morphology and biochemical characteristics. J Mol Cell Cardiol 11:339, 1979

2

Cardiovascular Anatomy

PHILIP R. FOX
N. SYDNEY MOÏSE
HOWARD E. EVANS
SANFORD P. BISHOP

CLINICAL UTILITY OF CARDIOVASCULAR ANATOMY

Diagnosis and management of congenital and acquired heart disease are founded upon a sound working knowledge of basic cardiovascular anatomy.[1–4] Clinical abnormalities identified from the history, physical examination, and diagnostic tests must ultimately be equated to derangements in cardiac structure and function to ensure diagnostic accuracy, direct suitable treatment, and assess response to therapy. Accordingly, careful necropsy dissection (chapter 37) and study help correlate relevant anatomic and pathologic changes (chapter 36) with associated findings from radiography (chapter 7), echocardiography (chapter 8), computed tomography (CT) and magnetic resonance imaging (MRI) (chapter 10), and surgery (chapter 39).

The appearance, and consequently interpretation, of the heart and surrounding structures in the living animal are influenced by a number of factors: (1) imaging techniques, (2) effects of inspiration and expiration, (3) cardiothoracic motion, (4) body position, such as right or left lateral, ventrodorsal or dorsoventral recumbency, and (5) effects of extracardiac factors (e.g., obesity, effusions, masses, trauma). Thus, multiple tomographic planes (i.e., sagittal [medial], transverse, and frontal [dorsal]) should be incorporated to arrive at a composite anatomic assessment.

THE THORACIC CAVITY

The shape of the thoracic cavity varies greatly in dogs but is relatively more uniform in cats. It is enclosed by the thoracic walls laterally and the diaphragm caudally, and it opens cranially to the exterior through the thoracic inlet. The *thoracic inlet* is bounded laterally by the first pair of ribs and their costal cartilages, dorsally by the longus colli muscles, and ventrally by the manubrium and sternum; it contains the forward portion of the cranial mediastinum which encloses the trachea and esophagus (situated left lateral to the trachea); recurrent laryngeal, phrenic, and first thoracic nerves; common carotid and subclavian arteries; apices of pleural cavities; pleural cupulae; and projection of the thymus (Figs. 2–1, 2–2).[1]

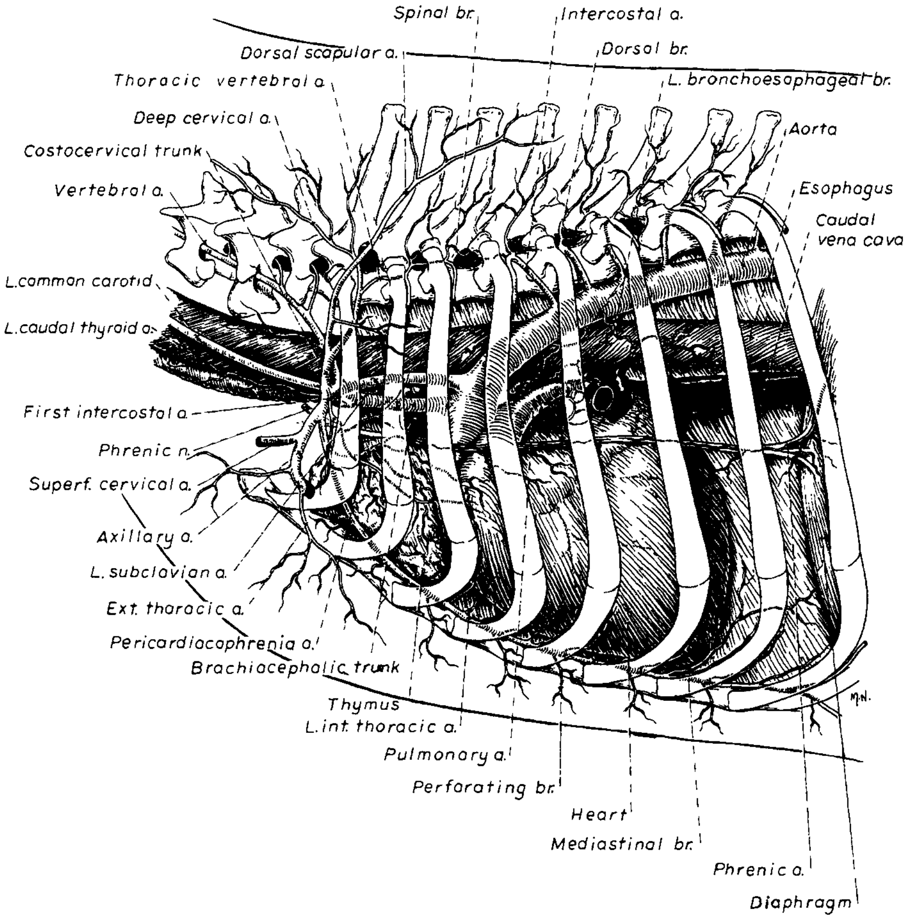


FIGURE 2–1

Anatomy of the thorax as seen from the left lateral projection. The lungs are not shown. Compare with Figure 2–2 to understand the orientation of structures and how they differ between the left and right lateral projections. (Reprinted with permission. Copyright 1993 by Howard E. Evans.)

THE MEDIASTINUM

The mediastinum is part of the extrapleural space within the thorax and divides the right and left hemithorax. It is covered and closed off from both pleural cavities by the mediastinal pleura and is open cranially to the deep fascial planes of neck musculature. The mediastinum is connected caudally to the retroperitoneal space through the aortic hiatus.[5, 6] It encloses the aorta, heart, trachea, esophagus, thymus, vagal and other nerves, and vessels entering into and exiting from the heart. The cranial mediastinal cavity lies in front of the heart and contains fat in obese animals; the middle mediastinal cavity contains the heart; and the caudal mediastinal cavity is behind the heart. The latter contains the descending aorta, the cranial vena cava, and the distal esophagus. In most dogs and cats the mediastinum is incomplete and permits air or fluid to pass between each hemithorax.

THE PERICARDIUM

This thin, strong fibrous sac lined by a serous membrane completely encloses the heart and a small quantity (0.2 to 5 ml) of fluid within the *pericardial cavity.* The *pericardium* is composed of an outer fibrous and inner serous component (the latter is divided into parietal and visceral layers). At the cardiac base, the fibrous pericardium blends with adventitia of the great arteries and veins that enter and leave the heart. The *epicardium* is the visceral layer of the serous pericardium, which is firmly attached to the heart muscle. The pericardium is elastic and capable of chronic distention to accommodate large volumes. More detailed information about its anatomy, vascular supply, innervation, and function is contained in chapter 29.

THE PLEURAE

Serous membranes line the walls of the thoracic cavity and cover the lungs and mediastinum. The pleurae form left and right pleural sacs that constitute the *pleural cavities*; in health, these are only potential spaces and contain a scant quantity of fluid that serves to lubricate the visceral and parietal pleural surfaces during respiration. When air or effusion collects between visceral and parietal pleurae in disease states, the pleural space and cavity enlarge.[7]

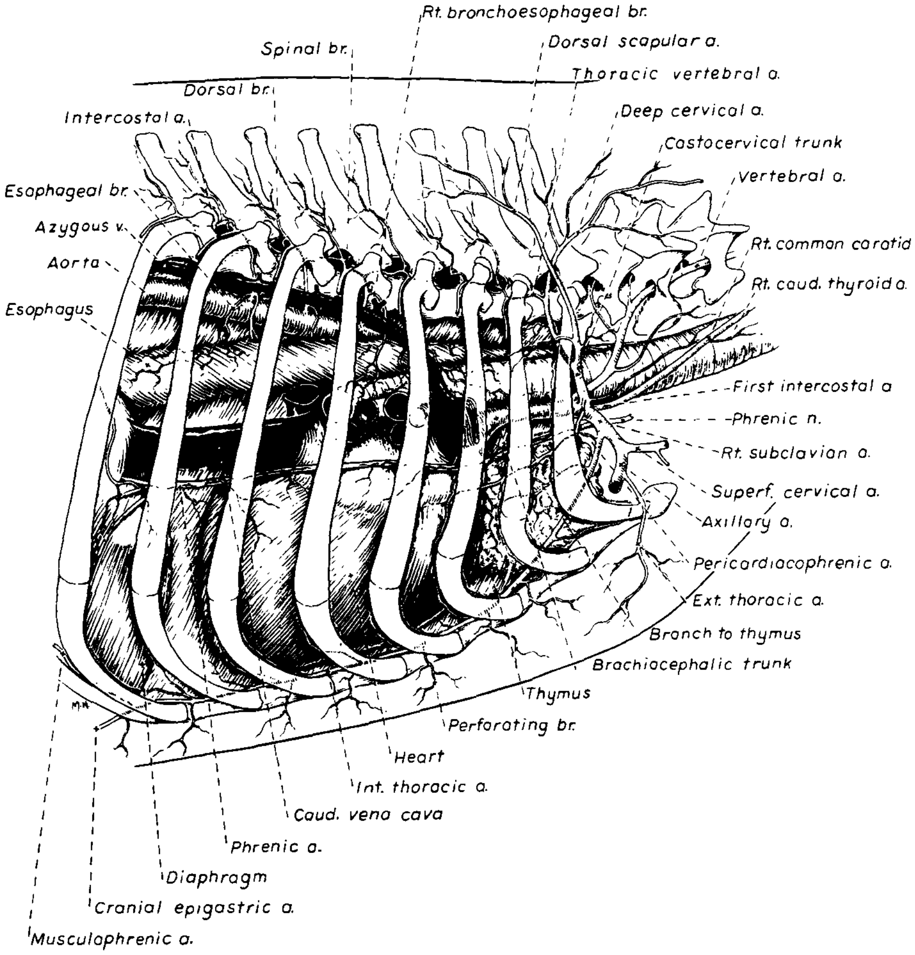


FIGURE 2–2

Anatomy of the thorax as seen from the right lateral projection. The lungs are not shown. Compare with Figure 2–1 to understand the orientation of structures and how they differ between the left and right lateral projections. (Reprinted with permission. Copyright 1993 by Howard E. Evans.)

THE LUNGS

The left lung is composed of a cranial lobe that is divided into cranial and caudal portions, and a caudal lobe. The left cranial lobe extends beyond the first pair of ribs into the pleural cupola and somewhat to the right of the medial plane. The right lung is composed of cranial, middle, caudal, and accessory lobes. Lung lobes overlap each other significantly.

The *pulmonary trunk* carries nonoxygenated venous blood from the right ventricle to the lungs. It arises from the fibrous pulmonary ring at the distal right ventricular outflow tract and bifurcates at the respective lungs into the left and right pulmonary arteries. *Pulmonary veins* return oxygenated blood from the lungs into the dorsum of the left atrium. Pulmonary veins generally lie ventral to the pulmonary arteries.

THE HEART

The heart is a muscular pump divided into four chambers by cardiac valves and septa. It is situated between the third and sixth ribs, and is largely covered by the lungs. On the right side, an upside-down, V-shaped region, the "cardiac notch," is formed by the lungs, which allow a small region of the pericardium to contact the lateral chest wall. In the dog, this occurs between the right 4th to 5th intercostal spaces; its dorsal apex is opposite the beginning of the distal 4th of the 4th rib, approximately between the sternum and costochondral junction. *In situ*, the cardiac *base* is oriented dorsocranially and the cardiac *apex* is directed ventrocaudally, slightly to the left of a transverse plane through the diaphragm (Figs. 2–1, 2–2). The cranioventral right ventricle and caudodorsal left ventricle are separated by the longitudinally situated and somewhat curved *interventricular septum*, which forms the division between ventricles, the blood-pumping chambers. Each is transversely divided into blood-receiving chambers—the left atrium that receives blood from the lungs, and the right atrium that receives blood from the rest of the body.

The heart is composed of three layers. The *myocardium* comprises the cardiac muscle. The *endocardium* lines the atrial and ventricular cavities. The *epicardium* is the most external layer and covers the myocardium.

IN SITU ORIENTATION

Viewing the heart *in situ* helps one understand relationships between various structures (Figs. 2–1, 2–2). Radiographic and echocardiographic anatomy and interpretation is greatly enhanced by an appreciation of these relationships.

EXTERNAL CARDIAC ANATOMY

Cardiac orientation is facilitated by observing the locations of the left and right auricles and coronary arteries.[1–3] The coronary groove encircles the heart except for the cranioventral aspect associated with the dorsal part of the right ventricle (pulmonary conus), and it separates the atria and ventricles. From the ventrocranial view, the left and right atrial appendages are seen on either side of the pulmonary artery trunk and aortic root (Fig. 2–3). The right ventricular outflow tract and main pulmonary artery are most prominent from this view, whereas the aortic root lies deep to the pulmonary trunk. The right ventricular free wall normally extends two thirds to three quarters of the distance from the coronary groove to the apex of the heart. The *cardiac apex* is formed by the left ventricle. The left anterior descending coronary artery courses from its origin at the aortic root, between the pulmonary artery and the left atrial appendage, and diagonally crosses the heart toward the apex. Several diagonal branches course over the free wall of the left ventricle and, to a lesser extent, the anterior portions of the right ventricular free wall.

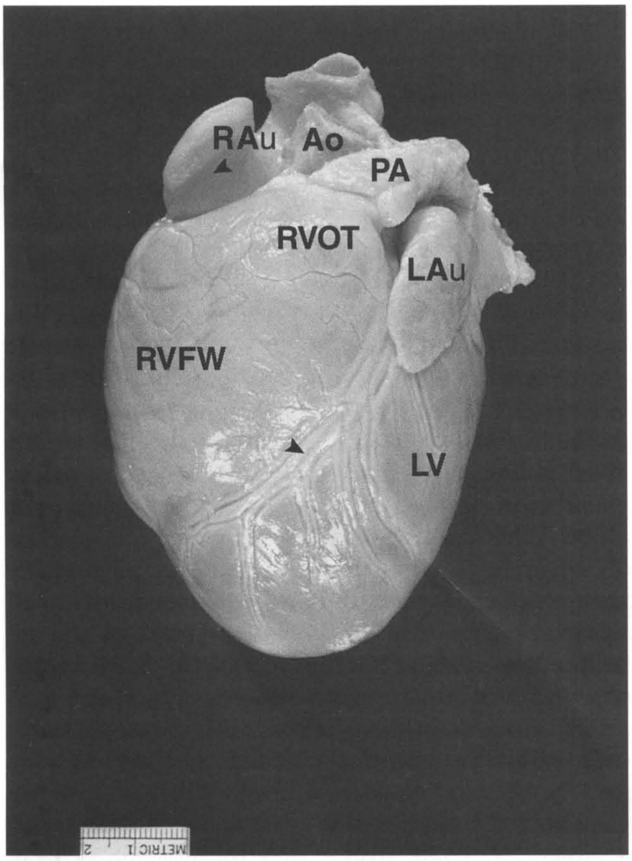


FIGURE 2–3

Ventrocranial view of the normal external anatomy of the canine heart. The cranial cardiac "waist" is represented by the main pulmonary artery *(PA)*, right auricle *(RAu)*, and ascending aorta *(Ao)*. The left coronary artery gives off a paraconal interventricular branch that accompanies the great coronary vein in the paraconal groove *(arrowhead)*. This marks the division between the right ventricular free wall *(RVFW)* and the left ventricular free wall *(LV)*. *LAu*, left auricle; *RVOT*, right ventricular outflow tract.

From the dorsocaudal view, the circumflex branch of the left coronary artery courses caudally in the left coronary groove between the left atrium and left ventricle and is visible on the caudal left ventricular wall (Figs. 2–4, 2–5). The right coronary artery extends caudally in the right coronary groove under the right auricle, sending marginal branches to the free wall of the right ventricle. The arteries and coronary arteries are shown in Figures 2–3, 2–4, and 2–5. The prominent sinus node artery (Fig. 2–4) courses from the caudal portion of the right ventricular free wall and dorsally over the right atrial free wall to the junction of the cranial vena cava and the right atrium. It extends through this junction, within or adjacent to the sinus node, and is a useful landmark for identification of the canine sinus node.

The veins entering the heart can serve as landmarks for internal structures. The caudal vena cava enters the right atrium at its caudal margin and is useful in identifying the opening of the coronary sinus and the fossa ovalis (Figs. 2–1, 2–2, 2–4). The cranial vena cava enters the dorsal aspect of the right atrium near the sinus node (Fig. 2–4). Pulmonary veins enter on the dorsal surface of the left atrium.

THE ATRIA

Both atria are relatively thin-walled structures. They act as reservoirs to receive blood from systemic (right atrium) or pulmonary (left atrium) circulations and then pump it into their respective ventricles. Each atrium has an associated auricular appendage (Fig. 2–4).

RIGHT ATRIUM

The right atrium (RA) lies dorsocranial to the right ventricle and receives blood from systemic veins and most of the heart (Figs. 2–4, 2–5*C,D*). An appendage, the *right auricle*, projects forward and downward, adjacent to the distal aspect of the RV outflow tract at the level of the pulmonary valves (Fig. 2–3, 2–5*A,B*). Its internal surface is composed of pectinate muscles.

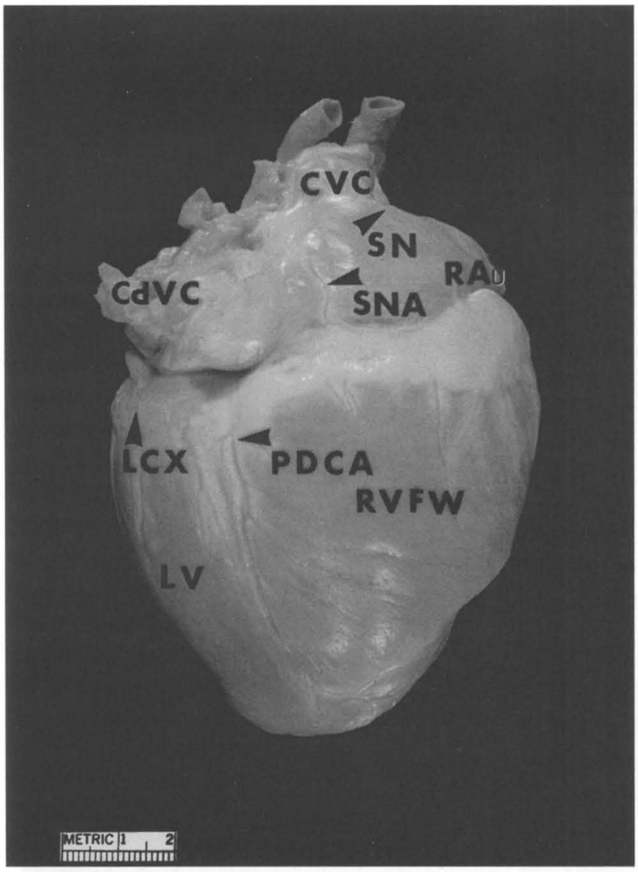


FIGURE 2–4

Dorsocaudal view of the normal external anatomy of the canine heart. The cranial vena cava *(CVC)* and sinus node artery *(SNA)* serve as landmarks for the sinus node *(SN)* (see text for details). The caudal vena cava *(CdVC)* enters the body of the right atrium; the right auricle (*RAu*) is seen at the cranial aspect of the right atrium (Fig. 2–3). The circumflex branch of the left coronary artery *(LCX)* and its subsinuosal interventricular branch *(PDCA)* are seen in their respective locations relative to the left ventricular free wall *(LV)* and right ventricular free wall *(RVFW)*. In the normal heart, the left ventricle forms the cardiac apex, which is observed in the ventrocranial (Fig. 2–3), dorsocaudal, and left lateral (Fig. 2–5*A,B*) views.

There are four openings into the RA (Figs. 2–5, 2–6): (1) the *cranial vena cava* enters the RA from the front and from above, draining the head, neck, thoracic limbs, ventral thorax, and adjacent abdominal wall; the azygos vein usually enters the cranial vena cava (although occasionally it enters the RA directly), draining part of the lumbar region and caudal thoracic wall; (2) the *caudal vena cava* enters the RA from behind and returns blood from the pelvic limbs, abdominal viscera, and part of the abdominal wall; (3) the *coronary sinus* enters the RA from the left and lies below the cranial vena cava; (4) the *right atrioventricular orifice* is surrounded by the right atrioventricular (tricuspid) valve and is situated between the RA and the right ventricle (RV). The *fossa ovalis* is a small depression on the medial RA wall located just caudal to the *intervenous tubercle*, a ridge of tissue situated between openings of the cranial and caudal vena cava (Fig. 2–5*C*).[8] It represents the fetal *foramen ovalis*, which permits RA to left atrium (LA) flow during fetal development and may be probe patent at necropsy in some animals.

LEFT ATRIUM

The LA forms the left dorsocaudal aspect of the cardiac base (Fig. 2–5*A,B*). The *left auricle* (lined with pectinate muscles) lies caudal to the pulmonary conus and trunk, which separates it from the cranially positioned right auricle (Fig. 2–3). Generally, two or three *pulmonary veins* from the left lung enter into the caudodorsal LA, and three from the right lung enter into the craniodorsal LA (veins from diaphragmatic lobes are largest and most caudal) (Fig. 2–5). The *left atrioventricular orifice* joins the LA and the left ventricle (LV) through the left atrioventricular (mitral) valve (Fig. 2–6).

INTERATRIAL SEPTUM

Separating both atria, this septum is marked with the fossa ovalis on its medial right atrial aspect. At its corresponding location on the medial side of the left atrial septum, a thin tissue flap representing the valve of the foramen ovale is located.

THE VENTRICLES

Both ventricles combine to confer a conical structure to the heart (Fig. 2–5). The right ventricle is cranioventral to the left ventricle. It receives systemic blood from the RA and pumps it through the pulmonary arteries into the lungs. The left ventricle normally constitutes the majority of cardiac mass. It receives oxygenated blood from the lungs by way of the pulmonary veins into the left atrium, and pumps this out of the aorta into the systemic circulation. Myocardial fibers form superficial, middle, and deep layers. The middle layer is the largest and conforms to a spiral or circular arrangement that interdigitates between both ventricles.

RIGHT VENTRICLE

The RV lies cranioventral to the left ventricle (Figs. 2–3 to 2–5). It appears crescent-shaped in cross-section, and its free wall is relatively thin compared with that of the left ventricle. Blood that fills the RV through the right ventricular inflow tract (the right atrioventricular orifice delineated by leaflets of the tricuspid, or right atrioventricular valve) is pumped out the RV outflow tract (*conus arteriosus*), across the pulmonary valves, and into the pulmonary arteries (Fig. 2–5*C,D*). A ridge of muscle, the *supraventricular*

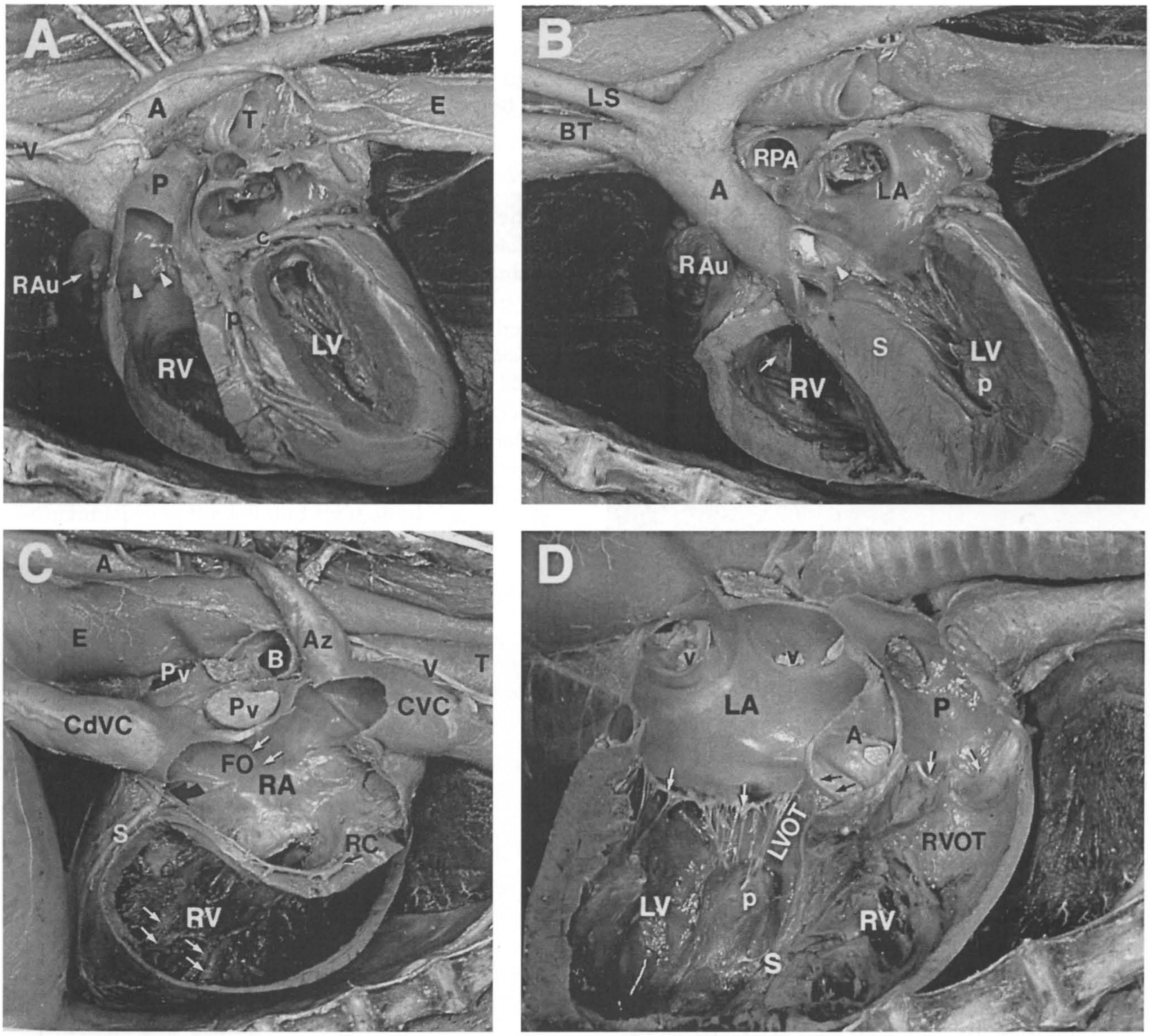


FIGURE 2–5

Composite of normal canine internal cardiovascular anatomy. Frames *A* and *B* are left lateral projections and frames *C* and *D* are right lateral projections. Frames *A* and *C* have intact major coronary arteries, but their supporting structures have been cut away in frames *B* and *D* to show the internal cardiac structures.

(A) The close proximity of the aorta *(A)* and pulmonary artery *(P)* is seen at the base of the heart. The main pulmonary artery *(P)* arises from the right ventricular outflow tract (see also Figs. 2–3, 2–5*D*), which is located dorsocranial to the body of the right ventricle *(RV)*. The position of the pulmonary valve semilunar cusps at the base of the pulmonary artery is indicated by *arrowheads*. The left coronary artery exits from the left coronary sinus. It branches into a paraconal interventricular branch *(p)*, which marks the division between the RV and left ventricle *(LV)*, and a circumflex branch *(c)*, which winds dorsocaudally and to the right across the caudodorsal heart surface in the coronary groove. At the subsinuosal (dorsal) interventricular groove, the circumflex branch courses toward the cardiac apex as the subsinuosal interventricular branch (see Fig. 2– 5*C*). *RAu*, right auricle; *T*, trachea; *E*, esophagus; *V*, vagal (X) nerve.

(B) The left heart is opened, exposing the LV inflow tract (i.e., the left atrioventricular orifice between the LA and LV delineated by leaflets of the mitral [or left atrioventricular] valve). The interventricular septum *(S)* separates the RV and LV. Just ventrocranial to the ascending aorta *(A)* lies the right auricle *(RAu)*. At the base of the aorta, one of the aortic valve semilunar cusps is indicated *(arrowhead)*. The parietal cusp of the tricuspid valve *(arrow)* delineates one border of the RV inflow tract. The LV inflow tract is delineated by the mitral valve. *LA*, left atrium; *RAu*, right auricle; *RPA*, right pulmonary artery; *LS*, left subclavian artery; *BT*, brachiocephalic trunk.

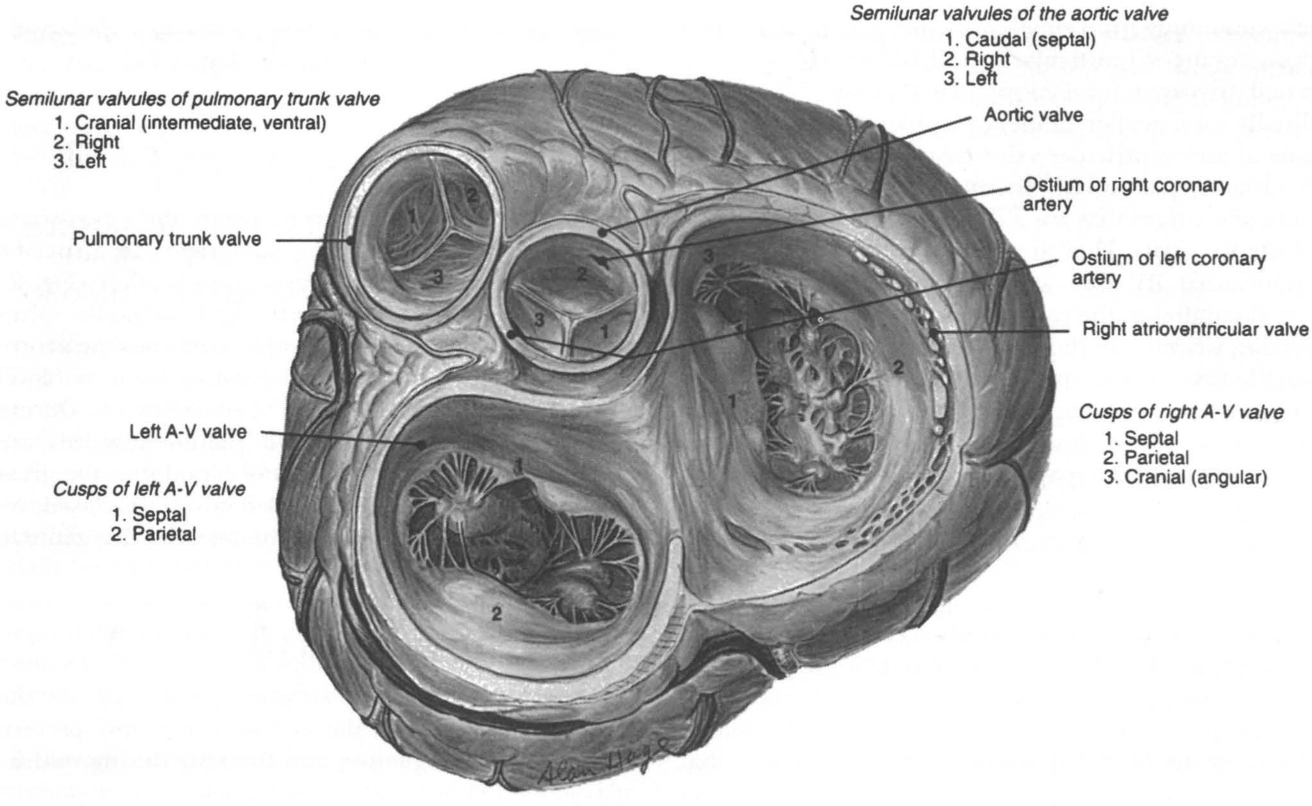


FIGURE 2–6

The base of the heart from the craniodorsal view. The great vessels and atria have been removed to show the cardiac valves. Valve leaflets and their relative positions are illustrated. (From Anderson WD, Anderson BG. Atlas of Canine Anatomy. Philadelphia, Lea & Febiger, 1994.)

crest, is situated obliquely between the atrioventricular opening and the origin of the conus arteriosus. *Papillary muscles* are conical, slender muscular projections from the RV wall that attach to chordae tendineae. Typically, papillary muscles originate from the apical third of the septal wall. Although often there are three major papillary muscles, the number and morphology (i.e., some may be fused or bifid) may vary, especially in cats. *Chordae tendineae* are fibromuscular strands usually arising from the apex of papillary muscles and

FIGURE 2–5 *Continued*

(C) The right coronary artery *(RC)* delineates the right atrium *(RA)* and RV. The caudal vena cava *(CdVC)*, cranial vena cava *(CVC)*, and azygos vein *(Az)* are seen entering the RA. The opening of the coronary sinus is indicated by a large, curved *arrow*. Below it the circumflex branch of the left coronary artery gives off the subsinuosal interventricular branch *(S)* at the subsinuosal interventricular groove, and courses toward the cardiac apex. The fossa ovalis *(FO)* is a small depression on the medial RA wall located just caudal to the intervenous tubercle, a ridge of tissue *(small straight arrows)* situated between openings of the cranial vena cava and caudal vena cava. The RV contains trabeculae carneae *(straight arrows)* in contrast to the LV chamber whose endocardial surface is much smoother and generally lacks these muscular bands (compare RV and LV in Fig. 2–5*D*). Pulmonary veins *(Pv)* are seen entering the left atrium; *V*, vagus (X) nerve; *E*, esophagus; *T*, trachea; *B*, right mainstem bronchus; *A*, descending aorta.

(D) The RV and majority of the interventricular septum *(S)* has been removed to show the left ventricle *(LV)* and LV outflow tract. Papillary muscles *(p)* serve as attachments for chordae tendineae which are then fixed to mitral valve leaflets *(small white arrows)*. Ostia of pulmonary veins *(v)* are seen in the roof of the left atrium *(LA)*. Blood from the LA then passes into the LV inflow tract (through the left atrioventricular valve [*small white arrows*]) to the LV, where it is pumped out across the left ventricular outflow tract *(LVOT)* and into the aorta. The aortic root *(A)* is observed between the left atrium *(LA)* and main pulmonary artery *(P)*; the location of an aortic valve semilunar cusp is indicated by *two small black arrows*. Pulmonary semilunar valve cusps *(small white arrows)* are evident between the main pulmonary artery and right ventricular outflow tract *(RVOT)*, comprised largely of the conus arteriosus. (Modified with permission from Done SH, Goody PC, Evans SA, Strickland NC. Color Atlas of Veterinary Anatomy. The Dog & Cat. Vol 3. London, Mosby-Wolfe, 1996.)

less commonly from small, muscular ventricular septal protuberances (particularly chordae attaching to the septal tricuspid valve cusp). They generally arborize distally into smaller branches to blend into free margins of atrioventricular valve cusps. Their morphology is variable, particularly in cats. *Trabeculae carneae* are muscular ridges that are a distinguishing characteristic of the RV cavity. They are particularly common on the endocardial RV free wall surface, are generally oriented parallel to the cardiac axis, and coalesce apically in the vicinity of the interventricular groove. Conductile tissue containing Purkinje's fibers and bundled into one or more delicate, branching strands, or *trabeculae septomarginalis* (moderator bands), may bridge to the septal wall, to papillary muscles, or to the RV free wall.

LEFT VENTRICLE

The LV is a conical chamber characterized by a relatively thick wall, the apex of which comprises the apex of the heart, and a relative lack of trabeculae carneae (Fig. 2–5). The anterior mitral valve leaflet separates the LV inflow and outflow tracts. Blood that fills the LV through the left ventricular inflow tract (the left atrioventricular orifice delineated by leaflets of the mitral, or left atrioventricular, valve) is pumped out through the LV outflow tract, across the aortic valve cusps, and into the ascending aorta (Fig. 2–5*D*). Generally, there are two papillary muscles—one dorsal (caudally situated) and one ventral (more cranially situated)—originating near the LV apex. Chordae tendineae attach to atrioventricular valve leaflets and arborize as described for the right ventricle. One or more trabeculae septomarginalis (moderator bands) may be present, and in cats, a wide variation in numbers and morphology may occur.

INTERVENTRICULAR SEPTUM

Separating the RV and LV, this septum is mostly composed of a thick, muscular part and a very small, thin, basal membranous region. In general the muscular portion is of similar thickness to the LV free (caudal) wall.

FIBROUS CARDIAC SKELETON

At the cardiac base, a "skeleton" of fibrous tissue composed of collagen and some cartilage separates atrial and ventricular myocardium. The specialized conduction fibers in the atrioventricular bundle extend through it from the atria to the ventricles.[9] This skeleton forms two fibrous rings. The *atrioventricular fibrous rings* surround each atrioventricular orifice; the others in the form of two scalloped rings surround the aortic (*aortic fibrous ring*) and pulmonary (*pulmonary fibrous ring*) orifices, respectively (Fig. 2–6).

CARDIAC VALVES

The four cardiac valves attach to their respective fibrous rings (see preceding paragraph) in a specific anatomic arrangement relative to each other (Fig. 2–6). During diastole, the aortic and pulmonic valves close first to prevent regurgitation back into the ventricles. Then, the atrioventricular valves open as blood travels from the atria to fill the ventricles. During ventricular systole, aortic and pulmonic valves are opened by ventricular ejection of blood into the great vessels, while the atrioventricular valves are closed, restrained from billowing into the atria by the chordae tendineae.

ATRIOVENTRICULAR VALVES

These valves line the atrioventricular ostia of the right and left ventricular inflow tracts and prevent blood from regurgitating into the atria during ventricular systole. They are attached at their external perimeter to collagenous *atrioventricular fibrous rings* surrounding each atrioventricular orifice, and at the ventricular surfaces of the valvulae by chordae tendineae (Figs. 2–5, 2–6). The *tricuspid valve (right atrioventricular valve)* consists of a dorsal septal cusp attaching to the ventricular septum and a ventral parietal cusp attaching to the right ventricular ventral (free) wall. Occasionally, small secondary cusps are present at the cusp extremities. The *mitral valve (left atrioventricular valve)* is similar but more robust than the tricuspid valve. Division into distinct cusps is less obvious than for the tricuspid valve, but septal and parietal divisions can be recognized.

AORTIC AND PULMONARY VALVES

Sometimes referred to as semilunar valves, the aortic and pulmonary valves are attached to their respective fibrous rings. Each semilunar valve consists of *right, left* and *septal semilunar cusps,* or valvulae composed of a fibrous tissue stroma covered by endothelium (Figs. 2–5, 2–6). The *aortic valve* lies caudal to the pulmonary valve. The free margin of each valvulae consists of crescent-shaped *lunulae,* and at the center of each valvule is a *nodule* that functionally occludes the space formed by the three contiguous semilunar cusps when these valves are closed in diastole. The aortic wall is dilated just peripheral to each cusp to form three *aortic sinuses* (the right, left, and septal sinuses). This widening of the base of the ascending aorta is the *aortic bulb.* The *right* and *left coronary arteries* originate from these right and left coronary sinuses through

ostia, which in the dog may be single or multiple.[10] The *pulmonary trunk valve* lies cranial to the aortic valve and is morphologically similar, albeit less robustly developed and without a distinct bulb.

CARDIAC BLOOD VESSELS

CORONARY ARTERIES

Coronary arteries supply blood to the myocardium. The *left coronary artery* exits from the left coronary sinus and branches (Figs. 2–3, 2–5*A*) into a cranial *paraconal interventricular branch* (formerly called left anterior descending coronary artery, cranial descending coronary artery, or dorsal interventricular branch of the left coronary artery); it courses obliquely and cranially on the left face of the heart, then rightward across the sternocostal surface in the paraconal interventricular groove.[11] It gives off left ventricular, right ventricular, and interventricular branches. A *circumflex branch* of the left coronary artery winds dorsocaudally and to the right across the caudodorsal heart surface in the coronary groove and has ventricular and atrial branches.[12, 13] At the subsinusal (dorsal) interventricular groove, it courses toward the cardiac apex as the *subsinusal interventricular branch* (formerly called dorsal interventricular branch of left coronary artery or posterior descending coronary artery) (Figs. 2–4, 2–5*C*). The *left marginal ventricular branch* courses down the left border of the left ventricle parallel to the subsinusal interventricular branch. In the dog, the left circumflex coronary artery and its branches supply the caudal left ventricle and a portion of the caudal right ventricular free wall. The *right coronary artery* is smaller than the left, originates from the right aortic sinus, and may give off many smaller ventricular branches that arborize in the RV wall (Fig. 2–5*C*). It curves cranioventrally and to the right in the coronary groove, covered dorsally by the right auricle. Rarely it extends to the borders of the right ventricle and supplies two thirds of the blood to the right ventricular free wall.[14] A small *accessory right coronary artery* was described in 20 percent of dogs.[15] An atrial branch of the right coronary artery supplies the sinoatrial node in dogs.[12, 15]

PULMONARY TRUNK

The *pulmonary trunk* and its branches transport unoxygenated (venous) blood to the lung. The trunk arises from the pulmonary fibrous ring at the conus arteriosus (Fig. 2–5*D*), where it is flanked by the left and right auricles, and then divides into the right and left pulmonary arteries. Just proximal to this bifurcation is the *ligamentum arteriosum*, representing the fetal ductus arteriosus. It extends from the aorta to the left pulmonary artery just as it branches from the main pulmonary trunk. Along its medial surface the pulmonary trunk contacts the aorta, and both vessels obliquely cross each other, forming a slight spiral. At its distal fourth, it is attached to the fibrous pericardium.

AORTA

The *aorta* is the thickest vessel and transports blood ejected from the left ventricle to systemic arteries that arise directly from it (Figs. 2–1, 2–2, 2–5*A,B*). The *ascending aorta* originates from its fibrous ring, turns abruptly dorsocaudally and to the left as the *aortic arch*, then courses caudally to its distal trifurcation as the descending aorta. At the aortic arch, blood is shunted to the head, neck, and thoracic limbs through two main arteries. The *brachiocephalic trunk* is the first large artery from the aortic arch and passes obliquely rightward and cranially across the ventral trachea. It gives off the *left common carotid artery*, the first branch to leave the brachiocephalic trunk, then the *right common carotid artery* and the right subclavian artery. Uncommonly, both common carotid arteries can arise from a common trunk off the brachiocephalic trunk.[16] The left subclavian artery branches off the aorta just distal to the brachiocephalic trunk.

CARDIAC VEINS

The *coronary sinus* represents the large, dilated terminal end of the great coronary vein, and it returns most of the blood that is supplied to heart. It empties into the right atrium ventral to the caudal vena caval opening (Fig. 2-5*C*) and may contain a small semilunar valve. The *great coronary vein* originates in the cardiac apex, ascends toward the base in the paraconal interventricular groove, follows the dorsal part of the coronary groove, and circles the diaphragmatic surface of the heart from the left. It collects a number of veins, including the *dorsal left ventricular veins* that ascend from the cardiac apex. The *middle cardiac vein* ascends the subsinuosal interventricular groove, collects veins from both ventricles, and empties into the coronary sinus. A number of other cardiac veins are variably present, and some ventral cardiac veins and small thebesian vessels open directly into the heart.[17]

LYMPH NODES AND VESSELS

The lymphatic system is an adjunct to the venous system. Lymph fluid ("primary lymph") escapes from capillaries and blood vessels into tissue spaces and is returned by afferent lymphatic channels to lymph nodes, which then act as filters and serve as lymphocyte germinal centers. Efferent lymph vessels exit from

lymph nodes carrying filtered lymph enriched with lymphocytes ("secondary lymph") and enter larger draining lymph vessels.[1]

Lymphatic drainage of the chest has been classified into parietal (lymph nodes of the dorsal and ventral thoracic lymph centers) and visceral (nodes of mediastinal and bronchial lymph centers) groupings.[1] The ventral thoracic lymph center is represented by the cranial sternal lymph nodes. The dorsal thoracic lymph center consists of intercostal lymph nodes. The mediastinal lymph center comprises the cranial mediastinal lymph nodes (usually associated with large precardial vessels). Pulmonary lymph nodes, when present, lie in the dorsal surfaces of primary bronchi between right and left tracheobronchial nodes and the lung parenchyma. Right and left tracheobronchial lymph nodes are present lateral to their respective bronchus and, less commonly, on the trachea. The right node is ventral to the azygos vein while the left node has a similar relation to the beginning of the thoracic aorta. The middle tracheobronchial lymph node is the largest in the group and lies in the angle formed by the origin of the primary bronchi from the trachea and below the esophagus. It is V-shaped, its apex fitting into the angle formed by the tracheal bifurcation.

The *thoracic duct* is the primary channel for lymphatic return. It begins in the sublumbar region or between the diaphragmatic crura as a cranial continuation of the cisterna chyli and continues through the diaphragm as the thoracic duct. The location of its termination varies but it usually empties into an anterior venous site.[18–20]

CARDIAC CONDUCTION SYSTEM

The heart has a specialized conducting system composed of the sinoatrial node, the atrioventricular node, and the atrioventricular bundle of His. In addition, pathways for internodal conduction have been described.[21–23, 26]

SINOATRIAL (SA) NODE

The SA node forms a wedge-shaped group of cells set into the junction of the cranial vena cava, right auricular orifice, and body of the right atrium in the region of the *sulcus terminalis*, a poorly defined external groove that lies opposite the internal right atrial structure, the *crista terminalis* (a thick ridge of muscle between the cranial vena cava and atrioventricular opening) (Fig. 2–4). It is of variable length, tapering toward the caudal vena cava. The SA node is composed of histologically discrete, specialized cells that are responsible for initiating cardiac impulses. As with the atrioventricular node, the SA node has an abundant supply of adrenergic and cholinergic nerve fibers.[9, 21, 23]

ATRIOVENTRICULAR (AV) JUNCTIONAL AREA

This term describes the area of specialized conduction tissues that connects the atrial and ventricular myocardium. It can be subdivided into several anatomic zones, although the exact extent of these subdivisions requires more complete clinicoanatomic studies.[21, 23–25]

The AV node originates as a mass of Purkinje cells in the lower interatrial septal wall in the right atrial endocardium, situated at the apex of the *triangle of Koch*. The triangle base is formed by the coronary sinus; the triangle apex is formed by the fibrous commissure of the flap (the *tendon of Todaro*) protecting the openings of the caudal vena cava and the coronary sinus, and the attachment of the tricuspid valve septal leaflet. Thus, the AV node is just cranioventral to the coronary sinus opening and craniodorsal to the tricuspid valve septal cusp.[21, 24–26]

It courses forward, penetrating the fibrous cardiac base, and continues down into the ventricular myocardium. Here, the branching bundle is located on the crest of the muscular interventricular septum, immediately subjacent to the interventricular component of the membranous septum. It divides into the *right* and *left bundle branches*. The left ventricular specialized conduction tissues are immediately subendocardial on the ventricular septal surface in the left ventricular outflow tract; they cascade down the septum below the septal (caudal) semilunar aortic cusp in a fanlike fashion, into three broad divisions (anterior, posterior, and septal). The fibers arborize, spread to the ventricular free wall, and ramify into the myocardial tissue. The right bundle branch dips down into the ventricular septum subendocardially and continues as a thin, cordlike structure intramyocardially, ramifying distally.[22]

CARDIAC NERVES

Cardiovascular physiologic responses to pharmacologic and physiologic perturbations are related to selective distribution of autonomic fibers.[26–33] These actions are associated with parasympathetic and sympathetic nerves.

Parasympathetic nerves supplying the cardiovascular

system originate from cranial and sacral locations. Cholinergic outflow arises from vagal nuclei in the medulla oblongata, which decreases the rate of SA nodal discharge and slows AV nodal conduction. Preganglionic fibers pass to the heart in the cardiac branches of the vagal nerves and synapse in the heart with ganglionic neurons. Postganglionic neurons are also distributed to the atria and, to a much lesser degree, to ventricular myocardium (the ventricular conducting system is well supplied by cholinergic innervation). Cholinergic fibers to resistance vessels of the heart and lungs originate in the cranial parasympathetic fibers descending from the vagal nucleus.

Although overlap exists, some degree of sidedness is present in parasympathetic cardiac input.[26] Moreover, selective innervation exists to the SA and AV nodes from intracardiac ganglia.[27–33] Parasympathetic innervation to the sinus node is primarily supplied from fibers coming from the ganglia situated in the *pulmonary vein fat pad.* This fat pad is located between the cranial and caudal vena cava and adjacent to the right pulmonary veins. The SA nodal artery is apically positioned to this fat pad.[27] Primary parasympathetic innervation of the AV node is from the ganglia in another fat pad that overlies the entry of the coronary sinus into the caudal interatrial septum at the junction of the caudal vena cava and caudal left atrium.[27, 28] Within both of these fat pads the ganglia are immersed in fatty tissue and close to the epicardial surface.[34, 35] In addition to parasympathetic fibers within these fat pads, nonadrenergic noncholinergic fibers have also been identified in the dog.[36] The right vagal nerve (Fig. 2–5) affects the sinus node more than the AV node, and the left vagal nerve affects the AV node more than the sinus node.[26] The ventricles do have parasympathetic innervation with fibers traveling intramurally or subendocardially, which then rise to the epicardium at the AV groove.[37]

Sympathetic nerves to the heart and vessels originate in the lateral reticular formation in the vasomotor center. Postganglionic sympathetic nerves impinge on the SA and AV nodes and innervate atrial and ventricular myocardium. Activation increases heart rate and contractility. Resistance blood vessels, splanchnic blood vessels, and cutaneous veins are especially densely innervated and when stimulated, effect strong vasoconstriction.

Cardiac sympathetic innervation is regional and based on input from extrinsic and intrinsic cardiac neurons.[38] Efferent sympathetic impulses reach the canine ventricle from the *ansae subclaviae* via branches of *cervicothoracic ganglia* (previously called the *stellate ganglia*) and *middle cervical ganglia.* Several sympathetic nerves from these ganglia then innervate relatively localized regions of the heart, with the *recurrent cardiac nerve* supplying the right ventricle and the *ventrolateral cardiac nerve* supplying the left ventricle. Sympathetic nerves innervating the intraventricular regions primarily follow the coronary arteries. Moreover, sympathetic afferent and efferent nerves travel within the first millimeter of the subepicardium, except in the right ventricular outflow tract where the fibers are subendocardial.[37]

REFERENCES

1. Evans HE. Miller's Anatomy of the Dog. 3rd ed. Philadelphia, WB Saunders, 1993
2. Anderson WD, Anderson BG. Atlas of Canine Anatomy. Philadelphia, Lea & Febiger, 1994, p 417
3. Done SH, Goody PC, Evans SA, Strickland NC. Color Atlas of Veterinary Anatomy. The Dog & Cat. Vol 3. London, Mosby-Wolfe, 1996
4. Field HE, Taylor ME, Butterworth BB. Atlas of Cat Anatomy. Chicago, University of Chicago Press, 1969
5. Koch T, Sajonski H. A contribution to the comparative-topographical anatomy of the mediastinum and the serous membrane covering the esophagus in man and dog (German). Zentralbl Vet Med 1:469, 1954
6. Preuss F, Henschel E. Praktikum der angewandten Veterinäranatomie. Berlin, Preuss and Henschel, 1967
7. Suter PF. Text Atlas. Thoracic Radiology. Thoracic Diseases of the Dog and Cat. Wettswil, Switzerland, Peter F. Suter, 1984
8. Dias SM, Orsi AM, Oliveria MC, et al. Sur la morphologie de la fosse ovale du coeur chez le chien adulte (*Canis familiaris*). Anat Hist Embryol 8:168, 1979
9. Baird JA, Robb JS. Study, reconstruction, and gross dissection of the atrioventricular conducting system of the dog heart. Anat Rec 146:313, 1950
10. Boucek RJ, Takashita R, Fojaco R. Functional anatomy of the ascending aorta and the coronary ostia (dog). Am J Anat 114:273, 1964
11. Christenson GC. The blood supply to the interventricular septum of the heart—a comparative study. Am J Vet Res 23:869, 1962
12. Kazzaz D, Shanklin WM. The coronary vessels of the dog demonstrated by colored plastic (vinyl acetate) injection and corrosion. Anat Rec 107: 43, 1950
13. Pianetto MB. The coronary arteries of the dog. Am Heart J 18:403, 1939
14. Donald DE, Essex HE. Pressure studies after inactivation of the major portion of the canine right ventricle. Am J Physiol 176:155, 1954
15. Moore RA. The coronary arteries of the dog. Am Heart J 5:743, 1930
16. Jarvis JF, Nell AMH. The brachiocephalic artery in the dog with special reference to the arterial supply of the esophagus. Anat Rec 145:1, 1963
17. Esperanca-Pina JA, Correia M, O'Neill JG, et al. Morphology of the vein draining the coronary sinus of the dog. Acta Anat 109:122, 1981
18. Kagan KG, Breznock EM. Variations in the canine thoracic duct system and the effects of surgical occlusion demonstrated by rapid aqueous lymphography, using an intestinal lymphatic trunk. Am J Vet Res 40:948, 1979
19. Huber F. Der ductus thoracicus. Inaugural dissertation. Dresden, 1909, p 1
20. de Freitas Von V, Piffer CR, et al. On the topography of the ductus thoracicus in the dog. Anat Anz 149:451, 1981
21. Nonidez JF. The structure and innervation of the con-

ductile system of the heart of the dog and rhesus monkey as seen with a silver impregnation technique. Am Heart J 26:577, 1943
22. Liu SK. Histopathologic study of the conduction system. *In* Tilley LP. Essentials of Canine and Feline Cardiology. 3rd ed. Philadelphia, Lea & Febiger, 1992, p 267
23. Yamaguchi A. Ultrastructure of the innervation of the mammalian heart. *In* Challice CE, Viragh S (eds): Ultrastructure of the Mammalian Heart. New York, Academic Press, 1973, p 27.
24. McGuire MA, de Bakker JMT, Vermeulen JT, et al. Atrioventricular junctional tissue discrepancy between histological and electrophysiological characteristics. Circulation 94:571, 1996
25. Ho SY, Kilpatrick L, Kamai T, et al. The architecture of the atrioventricular conduction axis in dog compared to man: Its significance to ablation of the atrioventricular nodal approaches. Cardiovasc Electrophysiol 6:26, 1995
26. Zipes DP. Genesis of cardiac arrhythmias: Electrophysiological considerations. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 5th Ed. Philadelphia, WB Saunders, 1997, p 548
27. Randall WC, Wursteer RD. Peripheral innervation of the heart. *In* Levy MN, Schwartz PJ (eds): Vagal Control of the Heart: Experimental Basis and Clinical Implications. Armonk, NY, Futura Publishing Co, 1994, p 21
28. Ardell JL, Randall WC. Selective vagal innervation of sinoatrial and atrioventricular nodes in the canine heart. Am J Physiol 251:H764, 1986
29. Randall WC, Ardell JL. Selective parasympathectomy of automatic and conductile tissues of the canine heart. Am J Physiol 248:H61, 1985
30. Butler CK, Smith FM, Nicholson J, et al. Cardiac effects induced by chemically activated neurons in canine intrathoracic ganglia. Am J Physiol 259:H1108, 1990
31. Takahashi N, Barber MJ, Zipes DP. Efferent vagal innervation of the canine left ventricle. Am J Physiol 248:H89, 1985
32. Randall DC, Randall WC, Brown DR, et al. Heart rate control in awake dogs after selective SA-nodal parasympathectomy. Am J Physiol 262:H1128, 1992
33. Plecha DM, Randall WC, Geis GS, et al. Localization of vagal preganglionic somata controlling the sinoatrial and atrioventricular nodes. Am J Physiol 255:R703, 1988
34. Randall WC, Ardell JL, Calderwood D, et al. Parasympathetic ganglia innervating the canine atrioventricular nodal region. J Auton Nerv Syst 16:311, 1986
35. Randall WC, Ardell JL, Wurster RD, et al. Vagal postganglionic innervation of the canine sinoatrial node. J Auton Nerv Syst 20:13, 1987
36. Ursell PC, Ren CL, Albala A, et al. Nonadrenergic noncholinergic innervation; anatomic distribution of calcitonin gene-related peptide-immunoreactive tissue in the dog heart. Circ Res 68:131, 1991
37. Ito M, Zipes DP. Efferent sympathetic and vagal innervation in the canine right ventricle. Circulation 90:1459, 1994
38. Yuan B, Ardell JL, Hopkins DA, et al. Gross and microscopic anatomy of the canine intrinsic cardiac nervous system. Anat Rec 239:75, 1994

3

Normal Cardiovascular Physiology

ROBERT L. HAMLIN

OVERVIEW OF THE CARDIOVASCULAR SYSTEM

The cardiovascular system circulates blood in order to supply oxygen and remove carbon dioxide from metabolizing tissues[1–4] (Fig. 3–1). The heart is actually composed of two pumps called the right and the left ventricles. The right ventricle pumps blood through the lungs and sucks blood from the systemic veins. The left ventricle pumps blood through the systemic circulation and sucks blood from the lungs. Valves within the veins and the heart keep blood flowing in one direction. The mitral and tricuspid valves prevent regurgitation from the ventricles into the atria, and the aortic and pulmonic valves prevent regurgitation from great arteries into the ventricles. Venous valves keep blood moving from capillaries toward the heart.

Most of the blood volume resides in systemic veins, whereas most of the interference to blood flow resides in systemic arterioles. Very little blood resides in the lungs or systemic capillaries. The capacity of the veins to store blood, and the interference to blood flow through arterioles, are determined by the degree of contraction or relaxation of the vascular smooth muscle surrounding the vessels. When vascular smooth muscle is constricted, venous capacity decreases and arteriolar resistance increases.

The blood volume and blood pressure in the pulmonary circulation, especially within the pulmonary capillaries and veins, depend upon the volume of blood within the systemic veins. If the blood volume is constant, then more blood resides within the systemic veins and less blood is available to reside within the pulmonary vessels. Venous and capillary blood pressures are correspondingly reduced. In contrast, the less blood within the systemic veins, the more blood resides within the lungs, and the greater are the pulmonary vascular pressures.

BLOOD VOLUME AND CIRCULATION OF BLOOD

The heart, blood vessels and lungs interact to exchange gases (oxygen and carbon dioxide) between the atmosphere and tissues. Distribution of blood to the systemic vascular beds depends on a number of factors, including blood volume, venous return, and cardiac filling.[1]

MICROCIRCULATION

The normal capillary microcirculation[5] is illustrated in Figure 3–2. At the capillary-alveolar level, serum moves across the capillary-alveolar membrane into the interstitium and back into the vascular system via lymph channels (chapter 13; see Figure 13–1). A hydrostatic force of 12 mmHg pushes serum through the alveolar-capillary membrane from capillary to interstitium. This results from (1) a positive pressure of 7 mmHg in the pulmonary capillary due to the right ventricle pumping blood into that capillary; (2) effects of the left ventricle sucking blood out of the capillary; and (3) a force of −5 mmHg within the interstitium associated with the elastic lung recoil and tendency of the thoracic wall to expand.

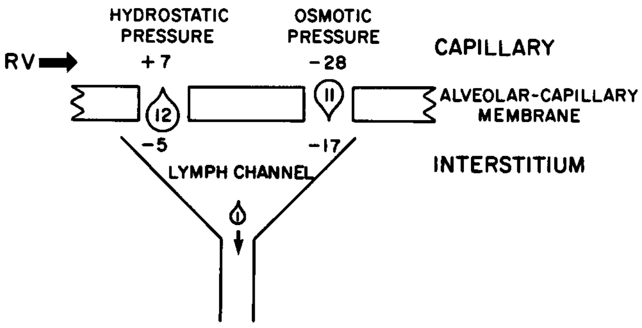


FIGURE 3–2

Schematic diagram of the alveolar-capillary membrane, with the capillary *(CAPILLARY)* situated above the membrane and the interstitial space *(INTERSTITIUM)* below. The right ventricle *(RV)* pumps blood through this capillary and generates a hydrostatic pressure of +7 mmHg. The osmotic plasma pressure (attributed to proteins) creates a force of −28 mmHg. Representative interstitial hydrostatic and osmotic (oncotic) forces are thus −5 and −17, respectively. By summing all the forces that either push serum out (12 mmHg) or pull serum in (11 mmHg) across the capillary pores, a net force of 1 mmHg is driving serum out of the capillary and into the interstitium. Once the serum reaches the interstitium, however, it is drained by the lymphatics back into the vascular system. Although no excess fluid builds up within the interstitium, the interstitium is continually bathed with serum.

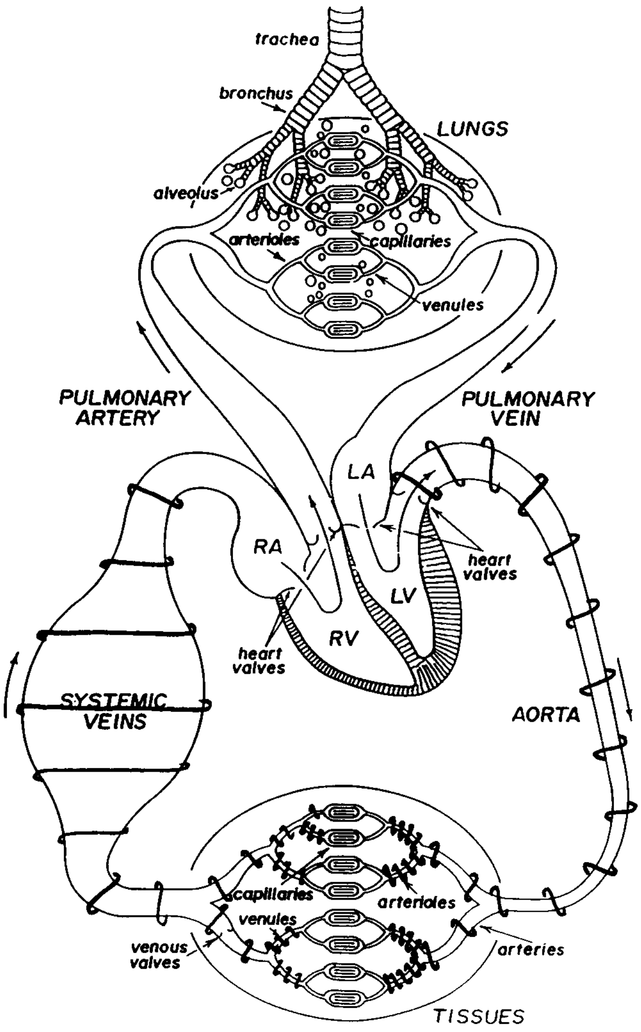


FIGURE 3–1

Diagram of the cardiovascular system. Vascular smooth muscle "wraps" around the systemic veins, aorta, and arterioles. The relative degree of vascular smooth muscle tone helps determine the volume of systemic venous blood, the effort required by the left ventricle to eject blood into the aorta, and the resistance to blood flow through systemic arterioles. If blood volume is constant, then the greater the systemic venous volume, the lesser the volume of blood—and pressure—within the pulmonary vessels. The volume and pressure of blood within the pulmonary capillaries and veins determine to what volume (i.e., the preload) the left ventricle fills. LA, left atrium; RA, right atrium; LV, left ventricle; RV, right ventricle.

Also, osmotic forces (actually oncotic forces because they are due to protein molecules) tend to retain fluid in both the capillary and the interstitium. Because proteins are in greater concentration in the capillary, the osmotic pressure is −28 mmHg; and, because there is less protein in the interstitial fluid, the osmotic force is only a −17 mmHg. Thus, a net osmotic force of 11 mmHg tends to force fluid from the interstitium to the capillary.

The total net effect resulting from 12 mmHg hydrostatic force driving fluid from capillary to interstitium, and −11 mmHg osmotic force tending to push fluid from interstitium to capillary, is approximately 1 mmHg. This drives fluid from the capillary to the interstitium, causing loss of serum to the pulmonary interstitium at a rate approximating 1000 ml per day.

Pulmonary lymphatics remove this fluid and return it to the vascular system. Therefore, there is neither gain nor loss of vascular volume. Figure 11–3 demonstrates what happens to the microcirculation when pulmonary capillary hydrostatic pressure becomes elevated owing to inadequate pulmonary circulation emptying in left-sided heart failure.

PRELOAD

The volume of blood within the pulmonary veins and capillaries is an important factor in the return of

blood to the left ventricle (LV).[6–9] This quantity of blood returning to the LV is termed the *preload.* It ultimately determines the resting length of sarcomeres and, thus, ventricular end-diastolic wall stress. Therefore, the state of systemic venous dilatation or constriction determines the left ventricular preload. All else being constant, if the systemic veins are dilated, left ventricular preload is reduced; if systemic veins are constricted, left ventricular preload is increased. A venodilator is a drug that relaxes the smooth muscle of systemic veins. Venodilators will therefore reduce left ventricular preload and are termed "preload reducers" (chapter 12).

There is an inverse relationship between the volume of blood within the systemic veins and the preload. The ventricular end-diastolic volume (preload) and thus, end-diastolic pressure, depends upon the ratio of blood volume to the capacity of veins to store it (the end-diastolic pressure also depends upon the force with which the atrium "kicks" blood into the ventricle during atrial contraction). The smaller the venous compartment, the more blood returns to the ventricles and the larger the preload.

The size of the venous compartment depends upon whether the smooth muscle in the walls of those veins is stimulated or is relaxed. If the systemic venous blood volume is great (i.e., blood "pools" in the systemic veins), then the volume of blood returning to the thorax and to the left ventricle is relatively small. If the volume returning to the ventricle is small, then ventricular preload is correspondingly small. A drug such as nitroglycerine that dilates veins (i.e., a *venodilator*) acts as a preload reducer; drugs that constrict systemic veins enhance preload.

AFTERLOAD

The degree of systemic arterial and arteriolar vascular smooth muscle constriction or dilatation is an important factor determining the afterload.[6–8] *Afterload* may be described as the tension, force, or stress acting on ventricular wall myocytes after onset of shortening. It indicates the degree of interference to blood flow from the LV to and through the systemic arterial tree, to the capillaries and through the veins. In general, if the vascular smooth muscle is relaxed (i.e., the arteries become less stiff and the arterioles dilate), the afterload will be reduced. In contrast, if the vascular smooth muscle is contracted (i.e., the arteries are stiffer and the arterioles are constricted), the afterload (and, thus, impedance to left ventricular emptying) will be increased.

A more complete discussion of preload and afterload follows (see dependency on preload, and dependency on interference of blood flow from ventricle to capillaries).

PRINCIPLES OF NORMAL CARDIOVASCULAR FUNCTION

To discuss the pathophysiology of heart failure (chapter 11), certain basic principles of normal cardiovascular function must be understood.[9] These include (1) heart rate, (2) force of ventricular contraction, (3) interference to blood flow, (4) myocardial stiffness or its reciprocal (i.e., compliance), (5) myocardial oxygen consumption (MVO_2), (6) microcirculation and transcapillary fluid movement into and out of the interstitial compartment, and (7) the cardiac cycle.

HEART RATE

Heart rate (HR) is determined by the rate of spontaneous sinoatrial (SA) nodal discharge. This in turn depends on existing autonomic efferent traffic to that structure (Fig. 3–3). Thus, SA discharge fluctuates according to the prevailing balance between parasympathetic nervous impulses (which slow SA nodal discharge) and sympathetic efferent impulses (which speed SA nodal discharge). In the normal dog, the SA node discharges approximately 100 times per minute, but this will vary between approximately 45 beats/min at rest to 259 beats/min during peak exercise.

PARASYMPATHETIC STIMULATION AND BLOCKADE

When vagal centers in the medulla oblongata are stimulated, acetylcholine (ACh) binds to its SA nodal receptor sites, decreasing the rate of SA nodal discharge. These receptor sites will be blocked from ACh by administration of a parasympatholytic drug such as atropine. Thus, while vagal stimulation decreases heart rate, vagal blockade by atropine increases it (usually to approximately 150 beats/min in dogs).

SYMPATHETIC STIMULATION AND BLOCKADE

When sympathetic centers in the medulla are stimulated, norepinephrine binds to its β_1-receptor site on the SA node, which increases the rate of SA nodal discharge. Certain adrenergic-blocking drugs such as atenolol, pindolol, and metoprolol are relatively cardioselective and block the β_1-receptor site. Other adrenergic-blocking agents, including propranolol, timolol, and esmolol, are nonselective and block both β_1- and β_2-adrenergic receptors. Thus, while β-adrenergic stimulation may speed the HR from a resting value of 60 to a stimulated level of 250 beats/min, β-adrenergic blockade may decrease the HR to 150 beats/min. Or

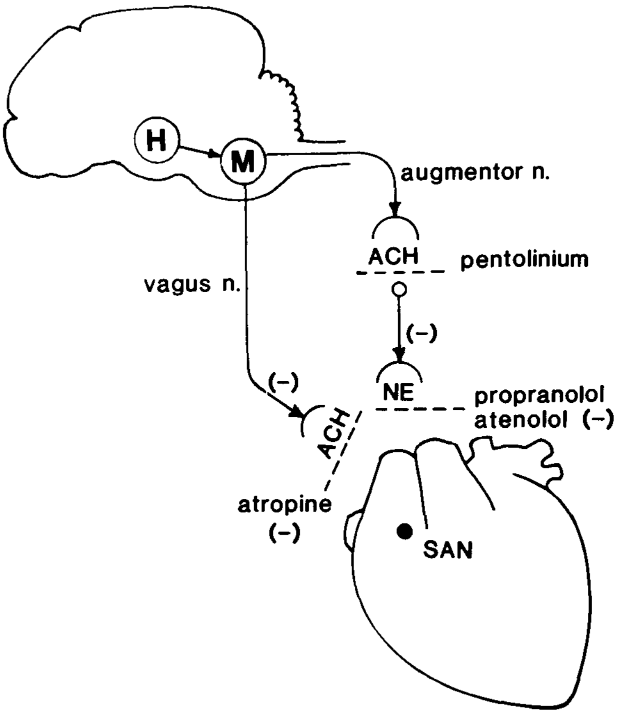


FIGURE 3-3

Efferent impulses arising from the medulla oblongata *(M)* and modulated by the hypothalamus *(H)* travel to the heart over the vagal (parasympathetic) and augmentor (sympathetic) nerves. Parasympathetic traffic slows the SA nodal discharge, slows AV nodal conduction, and decreases myocardial contractility. Sympathetic traffic causes opposite responses. Synapses for sympathetic traffic occur in the paravertebral ganglia. Its neurotransmitter is acetylcholine *(ACh)*, which is blocked by ganglionic blocking agents such as pentolinium. The postganglionic mediator for sympathetic efferent traffic is norepinephrine *(NE)*. This may be blocked by β_1-adrenergic blocking agents such as propranolol (a mixed β-blocker) or atenolol (a β_1-selective adrenergic blocker). The neurotransmitter for parasympathetic efferent traffic is acetylcholine, which may be blocked by atropine. SAN, sinoatrial node.

if the pet becomes slightly excited, HR may not increase as much with β-adrenergic blockade.

MEAN SYSTEMIC ARTERIAL BLOOD PRESSURE (MAP)

MAP is an important modifier of heart rate (Fig. 3–4). Both HR and MAP are related by a reflex that depends on pressure sensors within the aortic arch and carotid sinuses, which detect the level of blood pressure. These sensors send afferent volleys over the vagus and glossopharyngeal nerves to the brain. The brain then sends efferent volleys, predominantly over the vagus nerve, either to increase or slow the HR (Fig. 3–5). In general, when systemic arterial pressure is elevated, HR slows. Alternatively, when that pressure is reduced, HR increases.

This protective reflex tends to adjust blood pressure toward normal by changing HR, and thus, cardiac output, since cardiac output equals the product of HR

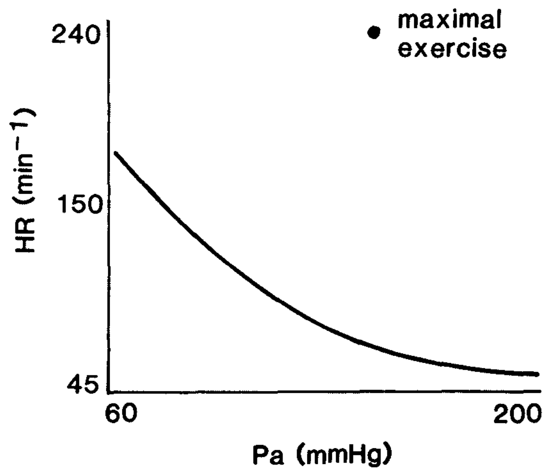


FIGURE 3-4

Illustration of the relationship between heart rate *(HR)* and arterial blood pressure *(Pa)*. Heart rate for most mammals varies between 45 and 240 beats/min, and mean systemic arterial blood pressure varies between 60 and 200 mmHg. During maximal exertion, heart rate is approximately 240 and mean systemic arterial pressure is approximately 150 mmHg. Under nonexercising conditions, heart rate slows as blood pressure elevates. This is known as the *Marey reflex*, mediated predominantly via the parasympathetic nervous system.

multiplied by stroke volume. The basic relationship between arterial blood pressure (ABP), cardiac output (CO), and total peripheral resistance (TPR) is APB = CO × TPR (chapter 35).

FORCE OF VENTRICULAR CONTRACTION

The force generated by the contracting myocardium depends on (1) the inotropic state (myocardial contractility, v_m); (2) the volume of blood within the ventri-

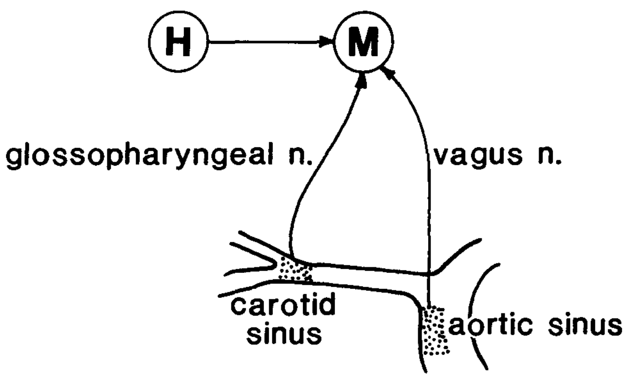


FIGURE 3-5

Tension (pressure) receptors at the aortic arch and carotid artery bifurcation send afferent impulses along the vagus and glossopharyngeal nerves to the medulla oblongata *(M)*. The intensity of these impulses is directly related to the pressure within the arterial tree. Input from the hypothalamus *(H)* modulates the afferent impulses from the baroreceptors.

cle just before it contracts (end-diastolic volume, EDV, also known as preload, PL); and (3) the interference to ejection of blood from the ventricle into the aorta, which is associated with afterload (AL) (discussed later).[6]

DEPENDENCY ON MYOCARDIAL CONTRACTILITY

The fundamental microscopic unit of cardiac muscle is the sarcomere (Fig. 3–6), millions of which are arranged both in series and in parallel to comprise the myocardium. However, true contraction results from cycling of heavy meromyosin heads (cross-bridges). These extend from the stationary myosin molecule to sites on the thin actin filaments that extend from the Z bands. When the heavy meromyosin heads cycle, they pull the opposing untethered ends of the actin filaments toward one another, which pull the Z bands on either side of the sarcomere.[9, 10]

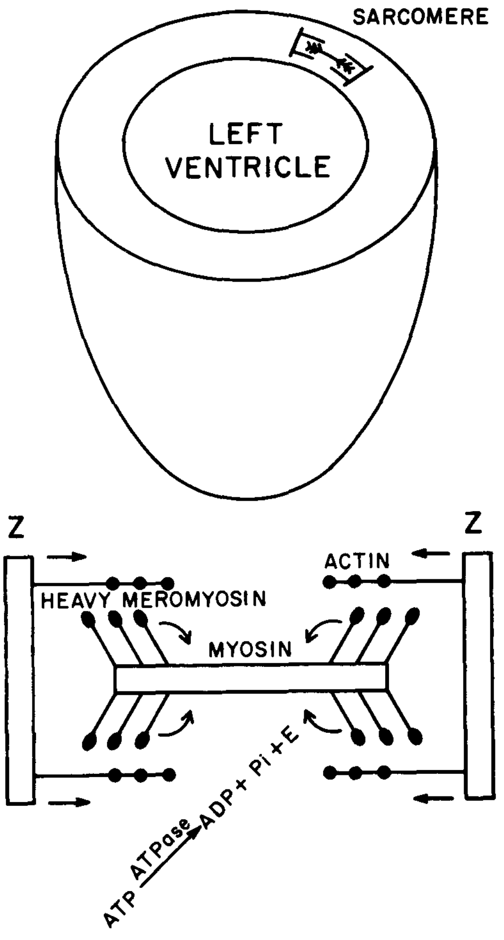


FIGURE 3–6

Diagram of the left ventricle with a single sarcomere *(top)* which is magnified *(bottom)* to illustrate its components. Millions of these sarcomeres comprise the myocardium and are responsible for contraction. See text for details.

EXCITATION-CONTRACTION COUPLING

Cycling of the heavy meromyosin heads[9] is initiated by the following sequence: (1) the myocardial cell is stimulated by any perturbation that increases conductance to Na^+ ions; (2) Na^+ ions rush from the outside to the inside of the cell, changing (depolarizing) the inside from a minus to a positive electrical charge; (3) depolarization increases conductance of the cell membrane to Ca^{++}, which enters the cell from the outside; Ca^{++} is also released from the sarcoplasmic reticulum where it has been concentrated; (4) Ca^{++} binds to troponin-c, which is attached to tropomyosin, and pulls the tropomyosin molecule from a position between actin and myosin that prevents the cross-bridges from cycling; (5) cross-bridges cycle, and the sarcomere either shortens or—if shortening is prevented—generates tension; (6) cycling is terminated when Ca^{++} is driven both back into the sarcoplasmic reticulum and outside of the cell, thus permitting the tropomyosin molecule to again inhibit the cross-bridges.

Energy required for cycling and for driving Ca^{++} against a concentration gradient into the sarcoplasmic reticulum comes from the hydrolysis of adenosine triphosphate (ATP) by ATPase, resulting in energy plus adenosine diphosphate (ADP) and inorganic phosphorus.

Once cycling of cross-bridges begins, the Z bands on opposite ends of each sarcomere are pulled toward one another. If motion is prohibited, the sarcomere will generate only tension. The maximal velocity with which each heavy meromyosin head cycles is termed *myocardial contractility,* or the *inotropic state,* and is represented by the symbol v_m. The inotropic state depends upon the rate of energy liberation when ATP is hydrolyzed by ATPase to ADP, releasing energy and inorganic phosphorus. The inotropic state is increased when norepinephrine, epinephrine, or sympathomimetic amines (e.g., isoproterenol, dopamine, dobutamine) bind to myocyte β_1-adrenergic receptors. Norepinephrine originates from sympathetic nerve endings, but epinephrine released from the adrenal medulla, which circulates to the receptors, has an identical inotropic effect. In contrast, the inotropic state is decreased by removing norepinephrine from the β_1-receptor or binding ACh to cholinergic receptors. Myocardial relaxation is more sensitive to ATP depletion than is the process of myocardial contraction. Thus, O_2 debt resulting in ATP depletion causes negative lusitrope earlier, and to a greater degree, than it causes negative inotrope.

DEPENDENCY ON PRELOAD

FRANK-STARLING LAW OF THE HEART

If all other factors are equal, the greater the volume of blood in the ventricle just before it contracts (i.e.,

the greater the preload), the more vigorous is the force of contraction.[4–6] This *Frank-Starling law of the heart* occurs because more cross-bridges are cycling, and there is a greater availability of Ca^{++} to initiate this cycling. This relationship is illustrated by the classic Frank-Starling curve (Fig. 3–7; see also Fig. 11–1*C*), in which a parameter of systolic (contractile) function (e.g., pressure-generated, stroke volume, or cardiac output) is plotted on the y-axis, versus preload (e.g., end-diastolic volume) plotted on the x-axis. Actually, x-axis units could be represented as numbers of cross-bridges cycling, or Ca^{++} available for cycle initiation; both relate to end-diastolic volume, end-diastolic fiber length, or ratio of the force distending the ventricle to the stiffness of the ventricle (chapter 11).

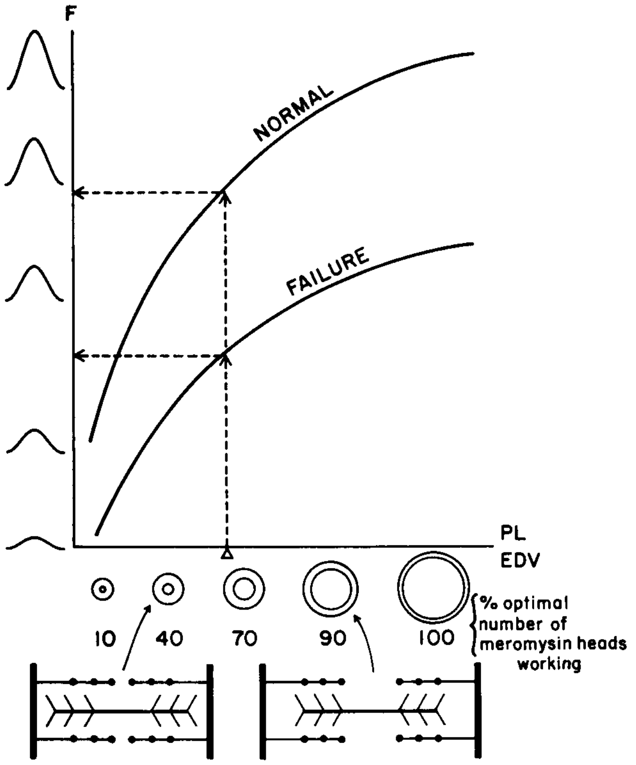


FIGURE 3–7

Drawing contrasting the relationship between preload and force of contraction. The Y axis (ordinate) plots the force (F) of contraction; the X axis (abscissa) depicts the volume of blood within the ventricle (i.e., preload *[PL]* or end-diastolic volume *[EDV]*) just before the ventricle contracts. The thick-walled circles below the abscissa depict the relative volume of blood within the ventricle as end-diastolic volume increases. Below each circle is the percent of total possible heavy meromyosin heads that can cycle at each corresponding ventricular volume. At the bottom are two sarcomeres. Left sarcomere shows that only one heavy meromyosin head per actin filament can cycle; right sarcomere shows that two heavy meromyosin heads can cycle. Thus, the sarcomere to the right generates more force but does not cycle more rapidly. The bottom curve represents the heart failure patient. Notice that at a given preload, the failing heart generates substantially less force of contraction compared with the normal heart. In heart failure, compensatory mechanisms increase preload in an effort to maintain force of contraction. This drives the Starling curve to the right and may ultimately result in pulmonary congestion.

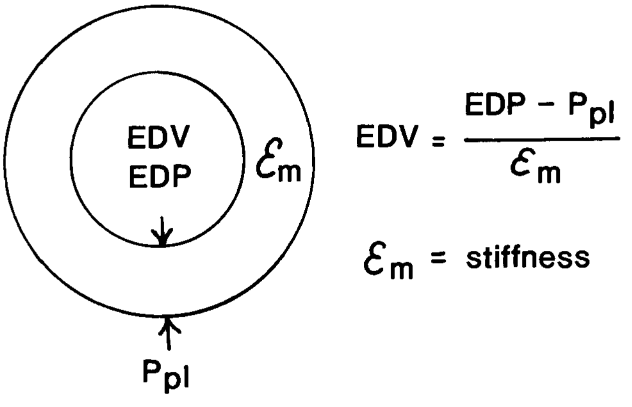


FIGURE 3–8

Schematic showing the relationship between ventricular blood volume at the end of diastole *(EDV)*, pleural pressures (P_{pl}), and myocardial stiffness (E_m). Ventricular blood volume just before contraction is determined by the pressure within the ventricle (i.e., end-diastolic pressure, or *EDP*) minus the pressure outside the ventricle (i.e., pleural pressure, or P_{pl}), all divided by the myocardial stiffness. The EDP is determined by blood volume and force of atrial contraction (i.e., atrial kick); pleural pressure is determined by lung function; myocardial stiffness is determined by disease, drugs, O_2 debt, fibrosis, and other factors.

MYOCARDIAL STIFFNESS

The myocardium may become stiff in a number of ways.[7, 9] If the intramyocardial vessels become full of blood, they may become rigid. Thus, elevation of right atrial pressure will cause the coronary circulation to become engorged, and both ventricles may appear stiff. Myocardium will also appear stiff if it contains or is surrounded by excessive fibrous connective tissue, since this tissue is normally stiffer than myocardium.

The ventricular stiffness (the reciprocal of which is compliance, or ventricular *lusitrope)* depends upon a number of factors. Most important is the rate and completeness with which Ca^{++} ions are driven off of troponin-c and are either resequestered into the sarcoplasmic reticulum or transported out of the myocyte. This activity is energy dependent and, thus, may become impaired if ATP hydrolysis and related energy release are reduced, as occurs with hypoxia.

The ventricular distending force (Fig. 3–8) is represented by the difference in ventricular pressure (end-diastolic pressure, EDP) minus the pressure outside the ventricle (intrapleural pressure, Ppl). Compliance also depends upon ventricular volume (preload). The larger the ventricular volume, the stiffer (i.e., the less compliant) the ventricle, and the greater the transmural pressure required to stretch the ventricle further.

Compliance is measured during diastole in a number of ways (Fig. 3–9): (1) as the ratio of end-diastolic ventricular volume to end-diastolic ventricular pressure; (2) as the maximal rate of fall of intraventricular pressure (dP/dt_{min}), which usually occurs during the isovolumetric relaxation period; (3) as Tau (T)—the

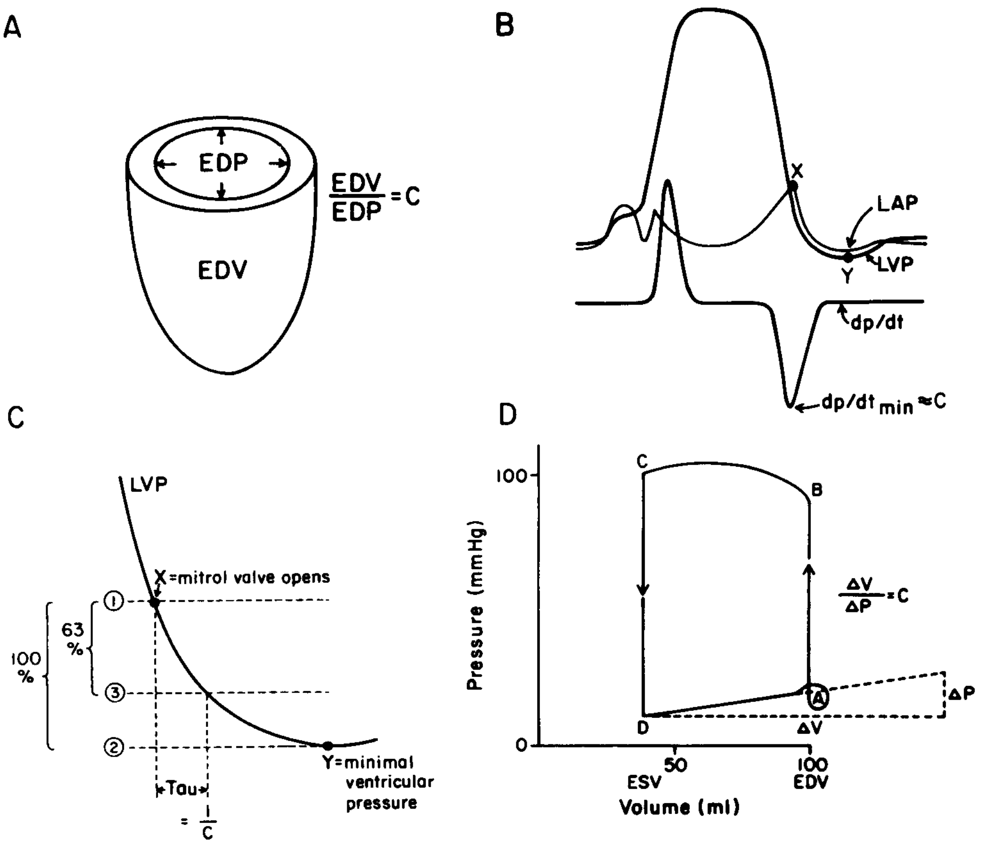


FIGURE 3–9

Methods of expressing myocardial or ventricular compliance *(C)*.

(A) Divide end-diastolic volume *(EDV)* by end-diastolic pressure *(EDP)*. Volume can be estimated by echocardiography, scintigraphy, or angiocardiography. Pressure can be measured by a high-frequency micromanometer inserted into the left ventricle via aortic or mitral orifices. Actually, this value occurs after the ventricle is completely filled. It is sensitive to both the rate and completeness of resequestration of Ca^{++} ions from troponin-c to sarcoplasmic reticulum *and* to the physical properties of the ventricular wall.

(B) Compare recorded left ventricular pressure *(LVP)* and its time-derivative (*dP/dt*, or change in pressure per change in time), using a high-fidelity micromanometer inserted into the left ventricle. Calculate the dP/dt by on-line analogue computer. The minimal point of dP/dt can be used to estimate compliance. Actually, this value always occurs before the ventricle begins to fill; therefore, it is most sensitive to the rate and completeness of sequestration of Ca^{++} ions from troponin-c to sarcoplasmic reticulum and may be relatively insensitive to filling of the ventricle. LAP, left atrial pressure.

(C) Tau (1/compliance) is the time required for ventricular pressure to fall 63% of the value (line 1 to line 3) from the pressure at which the mitral valve opens (*X*, line 1), to the lowest pressure it achieves in diastole (*Y*, line 2). This calculation, or a logarithmic function of this, is the most accurate method of expressing compliance.

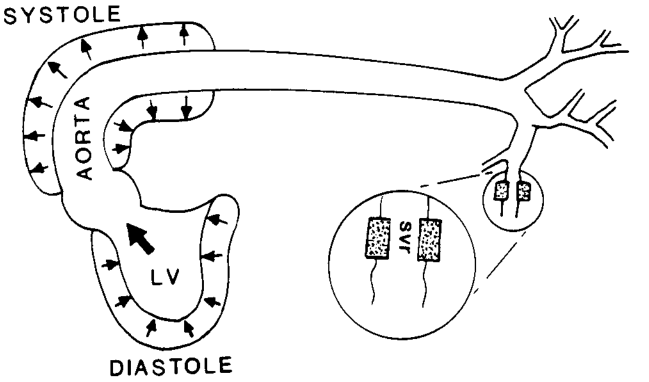
(D) The slope of the relationship between change in ventricular volume (ΔV) and change in ventricular pressure (ΔP) which occurs during diastole estimates compliance *C* at many instants during diastole. The pressure-volume loop is obtained by plotting ventricular pressure (ordinate) against ventricular volume (abscissa). Points for this loop are *A* = end-diastole; *B* = the instant the aortic valve opens; *C* = end-systole; *D* = the instant the mitral valve opens. ΔP is the pressure gradient required to fill the ventricle for the stroke volume; ΔV is the stroke volume. Because the slope of the line D–A is not constant, the "best" line is usually drawn.

duration in milliseconds required for intraventricular pressure to fall approximately 63 percent of its value from the instant the mitral valve opens, to when the most negative intraventricular pressure exists; and (4) as the slope of the curve when ventricular volume is plotted against ventricular pressure during ventricular filling.

Clinical examples of increased or apparent increased stiffness leading to reduced ventricular filling include feline hypertrophic cardiomyopathy, ventricular dilatation for any reason, myocardial fibrosis, pericardial tamponade, myocardial ischemia, and elevated intrapleural pressure.

VENTRICULAR INTERDEPENDENCE

Because both ventricles occupy space within the confines of the rather rigid pericardial sac, enlargement of one ventricle impinges upon the filling of the other ventricle and makes it appear stiff. This ventricular interdependence is important in understanding how, when one chamber becomes diseased (e.g., the left ventricle with mitral regurgitation resulting in left heart volume overload), the other ventricle may manifest altered diastolic function. In contrast, if a ventricle fills less completely than normal, then its force of contraction will fall according to the Frank-Starling relationship.



$$svr = \frac{\alpha_1 + PG_{F2} + O_2}{\alpha_2 + \beta_2 + V + PG_I}$$

FIGURE 3–10

Diagram illustrating factors relating to systemic vascular resistance (*svr*) and impedance. The left ventricle (*LV*) pumps blood into the initial portion of the aorta. The aorta expands to accommodate the blood but also impedes the flow of blood from the ventricle. Further resistance to blood flow occurs distally at the arterioles (*stippled*). Then, while the ventricle rests, the distended aorta recoils and propels the blood through the arterioles. The stiffness of the initial portion of the aorta generates impedance, and the aperture of the arterioles generates systemic vascular resistance. Both impedance and resistance are increased by α_1 stimulation and PGF_2; they are decreased by α_2, β_2, or vagal (*V*) stimulation, or by prostacyclin (PG_I).

DEPENDENCY ON INTERFERENCE TO BLOOD FLOW FROM VENTRICLE TO CAPILLARIES

The interference to blood flow[9, 10] from the ventricles to either aorta or pulmonary trunk is termed the *afterload* (AL). It must be appreciated that the left ventricle does not pump blood through the arterioles but only into the proximal portion of the aorta (Fig. 3–10). Then, while the ventricle is relaxed, the aorta, which has become distended by the left ventricular stroke volume, recoils and pumps the blood through the arterioles and capillaries to the veins. Thus, energy from the contracting ventricle and the blood it ejects is stored within the elastic elements of the aorta, to be dissipated by ejecting blood through the arterioles. At a given level of contractility, myocardial fiber shortening varies directly with PL and inversely with AL.

The AL depends upon the degree of contraction or relaxation of the vascular smooth muscle within the systemic arterial tree. When the smooth muscle is contracted, the arterial tree is stiff, and the ventricle perceives increased interference to ejection.

Factors Determining Vascular Smooth Muscle Constriction

Afterload[10] is measured in units of peak ventricular wall tension. *Laplace's law* approximates ventricular wall tension. Since the ventricle may be considered as a thick-walled sphere, tension (T) can be estimated by Laplace's formula:

$$T = P \times r/WT,$$

where P is pressure within the ventricle; r is the radius of the chamber lumen; and WT is the LV free-wall thickness. Clinically, afterload is often expressed as preload (PL) or end-diastolic volume (EDV), since PL or EDV is related to radius ($PL = 4/3 \text{ pi } r^3$) and is multiplied by ventricular pressure (P) divided by LV free-wall thickness (WT). Thus,

$$\text{Afterload} = PL \times P/WT.$$

The maximal value occurs at the instant the aortic valve opens; when the ventricle is at its largest end-diastolic volume; when the wall thickness is the least end-diastolic wall thickness; and when the ventricular pressure is great, although not maximal. That is, pressure still increases from the time the aortic valve opens until peak systole occurs. However, after the valve opens and the ventricle ejects, ventricular volume becomes smaller and the free-wall becomes thicker. Consequently, even though P increases, the ratio of PL × P/WT—and, thus, afterload—decreases.

Interference to blood flow from left ventricle to systemic capillaries is an important factor in afterload. It arises from two sources: (1) impedance (Z), and (2) systemic vascular resistance (svr).

Impedance is the sum of external factors opposing LV ejection and is closely related to afterload. It represents the ratio of aortic pressure to flow and is determined by physical properties of the vascular wall and blood (e.g., blood density and viscosity; aortic diameter and aortic wall viscoelasticity; reflected flow; and pressures generated in the distal arterial system). Impedance is estimated by dividing the pulsatile pressure in the aorta by the pulsatile flow.

Systemic vascular resistance is that interference imposed by having to force blood through the systemic arterioles. At rest, impedance contributes 15 percent of the interference to flow, while systemic vascular resistance contributes 85 percent. During maximal exertion, impedance may increase to 30 percent and svr decrease to 70 percent of the interference. Systemic vascular resistance is estimated by dividing the pressure difference between the aorta and right atrium by the cardiac output.

Blood viscosity[2, 5] also influences svr, since for any given arteriolar aperture, the more viscous the blood, the greater the pressure gradient required to drive blood across the aperture. Most of the blood viscosity depends upon the packed cell volume and is less dependent upon either the serum protein concentration or the erythrocyte foldability (erythrocytes, with a diameter of 8 μM, must fold to traverse a capillary with a diameter of only 5 μM).

Vascular wall tone is maintained by smooth muscle. The contractile state of smooth muscle cells responds to many vasoactive agents. These agents alter both impedance and systemic vascular resistance, as well as venous capacity. The net effect depends upon the drug and dose, the relative intensity of autonomic nervous stimulation, and the specific vascular bed affected (Table 3–1).

MYOCARDIAL OXYGEN CONTENT

The amount of oxygen present within the myocardium at any one time results from a balance between

TABLE 3–1
Responses of Vascular Smooth Muscle to Various Stimuli

Vasodilate	Vasodilate/ Vasoconstrict	Vasoconstrict
β_2-Adrenergic stimulation	α_2-Adrenergic stimulation	α_1-Adrenergic stimulation
Vagal stimulation	Dopamine	Serotonin
Bradykinin	Prostaglandin	Angiotensin II
Adenosine		Endothelin
Atrial natriuretic peptide		Vasopressin/ADH
Histamine		
Nitric oxide (EDRF)		
Acetylcholine		

EDRF, endothelin-derived relaxing factor; ADH, antidiuretic hormone.

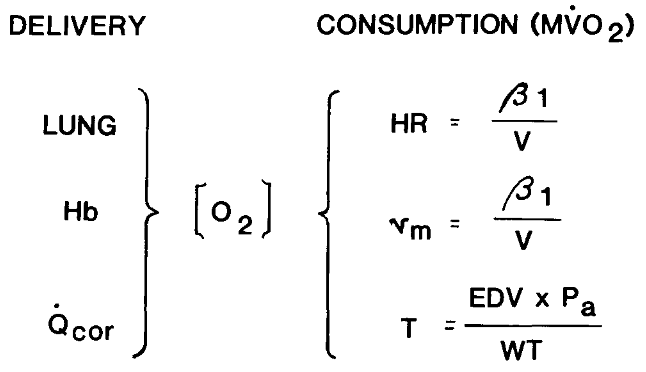


FIGURE 3–11

The amount of oxygen *(O_2)* present in the myocardium depends upon the balance between oxygen delivery and oxygen consumption *(MVO_2)*. Oxygen is delivered if the lung functions well, if the blood contains adequate amounts of normal hemoglobin *(Hb)*, and if the coronary blood flow *(Q_{cor})* is sufficient. Oxygen consumption depends mainly on three factors: heart rate *(HR)*, myocardial contractility *(Vm)*, and peak myocardial tension *(T)* generated during contraction. The former two factors are determined by a balance between β-adrenergic *(β_1)* activity, which increases O_2 demand, and vagal *(V)* activity, which decreases O_2 demand. Peak tension *(T)* is determined by end-diastolic volume *(EDV)* and diastolic systemic arterial blood pressure *(Pa)*. Peak tension is inversely related to the wall thickness *(WT)* of the chamber.

cardiac O_2 delivery minus cardiac O_2 extraction (Fig. 3–11).[10] The amount of O_2 extracted is termed *myocardial oxygen consumption* (MVO_2). Oxygen delivered to the heart depends on pulmonary function (an example of the interdependence between the heart and the lungs), the amount and quality of hemoglobin that carries O_2, and the coronary blood flow, which is dependent on forces driving blood through that circulation.

CORONARY BLOOD FLOW

Because of the importance of coronary blood flow, its major determinants must be summarized.[10, 11] As with any tube, the volume of blood flowing through the coronary circulation is a function of the pressure gradient between the two ends (i.e., the aortic pressure minus the right atrial pressure) (Fig. 3–12). However, because the coronary circulation flows through collapsible tubes that traverse the myocardium, ventricular contraction causes their compression and actually interferes with coronary blood flow. Thus, during ventricular systole, intramyocardial tension is great enough to terminate coronary blood flow, even though the pressure gradient between aorta and right atrium is still maintained. This is applicable principally to the left ventricular myocardium, which has greatly elevated intramyocardial pressure. During diastole, when the aortic valve is closed, aortic diastolic pressure is transmitted without impediment through the sinuses of Valsalva to the coronary ostia. Intramyocardial tension

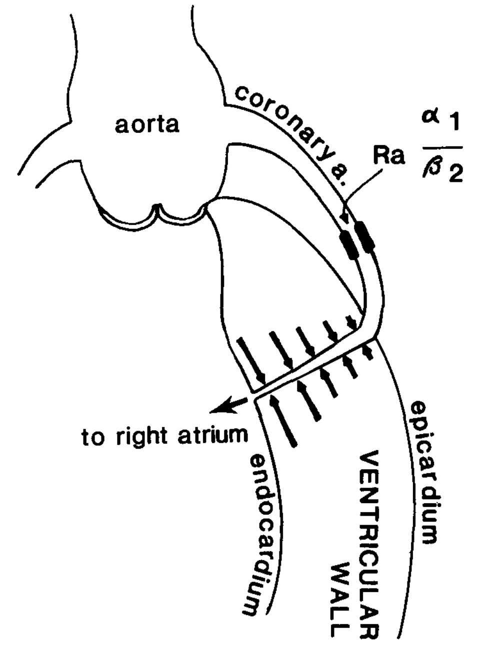


FIGURE 3–12

Drawing illustrating the factors effecting coronary blood flow. Coronary blood flow *(Q)* equals the driving force, that is, aortic pressure *(Pa)*, minus right atrial pressure *(PRA)*, divided by the resistance to flow by the coronary arterioles *(Ra)* plus compression of the coronary vessels by the contracting wall *(Rc)*. Coronary arteriolar resistance *(Ra)* is increased by α-adrenergic traffic (α_1); β_2-adrenergic efferent traffic (β_2) decreases that resistance. Note that the compressive forces on the coronary vessel become greater near the endocardium (larger arrows) than near the epicardium (smaller arrows). This is because intramyocardial tension is greater in the deeper regions of the ventricular wall than at the more superficial regions. Also, when heart rate becomes more rapid, average ventricular pressure is greater than when heart rate is slower.

falls precipitously, offering little resistance to intramyocardial coronary flow. Most coronary blood flow occurs during this period and is greatest whenever the heart spends more time in diastole.

Coronary vascular resistance is influenced by a number of factors. Neural influences are very important. For example, α_1- and α_2-adrenergic receptors release norepinephrine and cause coronary vasoconstriction. In contrast, β_1- and β_2-adrenergic receptors mediate vasodilation. Metabolic, myogenic, and pharmacologic factors are important, as are substances released from the endothelium causing vasodilation or vasoconstriction.

It follows that when the myocardium requires more O_2, efforts to slow the heart should improve coronary blood flow by increasing diastole. Oxygen debt could result by increasing heart rate and the time spent in systole.

Myocardial oxygen consumption is determined primarily by (1) heart rate, (2) myocardial contractility, and (3) myocardial tension. Heart rate and contractility are determined by the balance between β_1-adrenergic and vagal efferent activities. According to the Laplace relationship, peak myocardial tension is directly related to EDV and aortic diastolic blood pressure (Pa) but is inversely related to ventricular wall thickness (i.e., tension equals the product of intraventricular pressure and internal radius divided by the wall thickness). Thus, events that increase either EDV or Pa or that decrease myocardial wall thickness increase peak tension (and MVO_2). This emphasizes the importance of compensatory responses that decrease ventricular volume and aortic pressure and keep the ventricular wall thick by compensatory hypertrophy (chapter 11).

Two factors influencing myocardial oxygen consumption—heart rate and O_2 delivery (the duration of diastole)—can be synthesized in a parameter called *percentage diastole* (Fig. 3–13). The higher the heart rate, the greater the O_2 consumption and the less time there is for O_2 delivery. When heart rate speeds, systole shortens, but the number of systoles increases. Therefore, the time spent in systole increases. However, diastole shortens disproportionately more, so that the percentage of time spent in diastole falls precipitously.

THE CARDIAC CYCLE

The sequence of events that occurs during contraction and relaxation of the heart is termed the cardiac

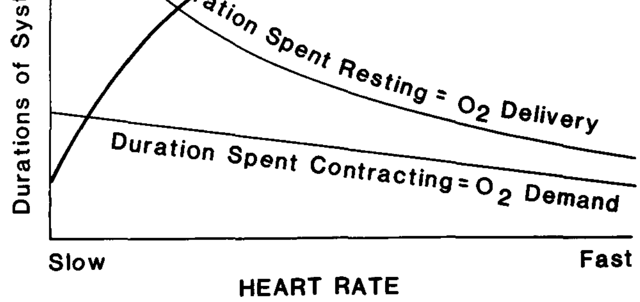


FIGURE 3–13

Illustration of the relationship between heart rate and duration of systole and diastole. Duration of systole and diastole (ordinate) are plotted against heart rate (abscissa). Duration in diastole represents the time that coronary blood flows and oxygen is delivered to the myocardium; the duration in systole represents the time that intramyocardial tension obstructs coronary flow and determines the demand of the myocardium for oxygen. Note the distinct advantage for myocardial oxygenation at slower heart rates.

cycle.[9–11] Since it occurs repetitively, we shall examine only a single cardiac cycle (Fig. 3–14*A*,*B*).

The cardiac cycle is initiated by the P wave of the electrocardiogram (ECG) (occurring before time interval I), which represents the wave of stimulation that drives the atria to contract. Between I and II the atrium contracts, atrial and ventricular pressures and ventricular volume increase slightly, the leaflets of the mitral valve open to accommodate flow from atrium into ventricle, and myocardial tension (T) increases slightly.

After blood enters the ventricle during atrial contraction, the ventricle reaches an elastic limit, suddenly

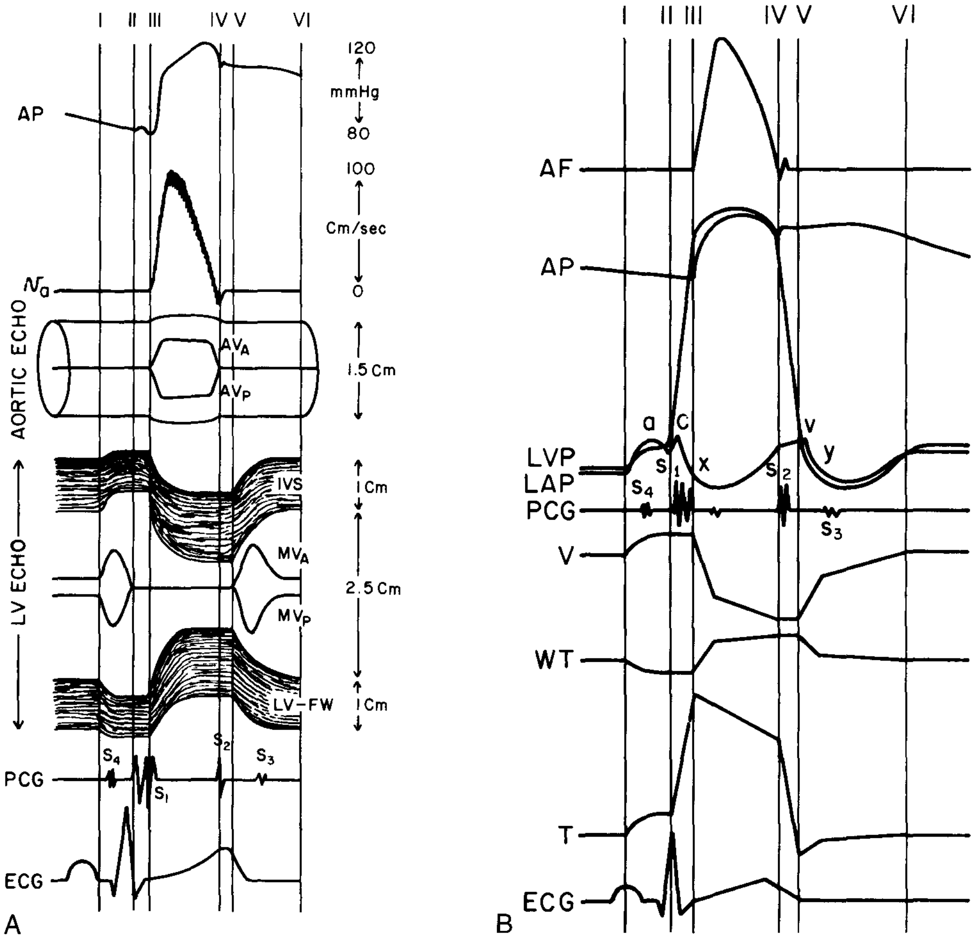


FIGURE 3–14

Graphs showing events of the cardiac cycle illustrated by echocardiography, pressure recordings, heart sound recording, and electrocardiography, as would occur in a large breed dog. Cardiovascular events may be timed with respect to the electrocardiograms *(ECG)* at the bottoms. Curves are relatively schematized, and the echocardiographic recordings are highly schematized. The figures show aortic flow *(AF)* and aortic velocity *(v_a)*; aortic pressure *(AP)*; pressures within the left ventricle *(LVP)* and left atrium *(LAP)*; heart sounds *(PCG)*: S_1 = first heart sound; S_2 = second heart sound; S_3 = third heart sound; S_4 = fourth heart sound (normally, only S_1 and S_2 are present); left ventricular wall thickness *(WT)*; left ventricular free-wall *(LV-FW)*; intramyocardial tension *(T)* [T = (LVP × V) / WT]; anterior and posterior leaflets of the aortic valve *(AV_A; AV_P)* and mitral valves *(MV_A; MV_P)*.

Cardiac cycle time intervals are labeled with Roman numerals (I–VI). They identify vertical time lines relative to each set of curves and physiologic activities to mark events as they relate to each other (see text for details).

- Interval I to II represents the period when the left atrium ejects blood into the left ventricle.
- Interval II to III is the period of isovolumetric contraction when the left ventricle is generating great force, but it is not ejecting blood because the pressure has not yet exceeded that in the aorta.
- Interval III to IV is the period of left ventricular ejection, which has initially a period of rapid ejection and then terminally, a period of reduced ejection.
- Interval IV to V is the period of ventricular filling, separated into the initial period of rapid filling and the terminal period of reduced filling.
- Following interval VI and until interval I of the next cardiac cycle, the heart is quiet. Nonetheless, the arterial tree is recoiling and moving blood through the arterioles and capillaries to the veins.

decelerates, and throws cardiohemic structures into oscillations, giving rise to the soft, low-pitched fourth heart sound (S_4).

Next, just before **II**, the QRS complex of the ECG signals the wave of stimulation of the ventricles, and at **II**, the ventricle begins to contract. Initially, ventricular contraction forcibly closes the mitral valve leaflets when ventricular pressure exceeds the relatively low atrial pressure. As these leaflets close and suddenly decelerate the blood in the ventricle as it "attempts" to re-enter the atrium, cardiohemic structures are again thrown into oscillations, giving rise to the first heart sound (S_1). The intensity of the first heart sound depends upon how vigorously the leaflets are closed and decelerate the blood. Ventricular pressure quickly rises to a level just less than that of aortic pressure. Ventricular volume does not change since the ventricle is closed at one end by the mitral valve and at the other end by the aortic valve. This period is termed the period of isovolumetric contraction because the ventricle is contracting but is not changing volume.

Next, as ventricular pressure continues to elevate (**II** to **III**) to levels greater than that within the aorta, the aortic valve is thrown open (usually in silence); blood is ejected first at a rapid rate and then at a reduced rate from left ventricle into aorta (**III** to **IV**). At the instant (**III**) the aortic valve opens—when the product of ventricular volume and ventricular pressure divided by ventricular wall thickness is always the greatest—myocardial tension reaches its maximum, termed the afterload (AL). Notice on the aortic echocardiogram that the aortic leaflets open as blood is ejected into the aorta. Notice also that aortic flow peaks during the early portion of ejection and then decreases suddenly until it approaches zero at **IV**. Occasionally, when blood flow into the aorta suddenly reaches its peak and then decelerates, there are oscillations of cardiohemic structures just after the first heart sound; normally, however, ejection occurs silently.

When ventricular relaxation begins (**IV**) and ventricular pressure plummets toward 0, the aortic valve slams closed because aortic pressure exceeds ventricular pressure. Aortic pressure is partially sustained due to the elastic recoil of the arterial tree, which squeezes the arterial blood and forces it through the systemic vascular resistance. Ventricular pressure falls first to a level below aortic pressure (**IV**), then to a level below atrial pressure (**V**). This period of ventricular relaxation, when pressure within is falling but the volume is not changing, is termed the period of isovolumetric relaxation.

When this period of isovolumetric relaxation ends, the leaflets of the mitral valve open (**V**), and blood flows quickly from atrium to ventricle. The ventricular filling is first rapid and then occurs at a reduced rate. When the ventricle converts from a chamber that fills first rapidly and then suddenly at a reduced rate, cardiohemic structures are thrown into oscillations, giving rise to the third heart sound (S_3). It is noteworthy that both the fourth and the third heart sounds are caused by the ventricle converting to a chamber that fills first rapidly, then at a reduced rate—the fourth sound in the wake of atrial contraction and the third sound in the wake of more passive filling.

Notice that at interval **V**, myocardial tension is actually a negative value. This is because the volume within the chamber is small, the wall is thick, and the pressure is low. Thus, according to Laplace's law, tension is at its lowest. This negative tension permits the ventricle to generate subatmospheric pressure and to suck blood through and from the atrium. The ventricle also sucks blood during contraction. When the ventricle ejects blood into the aorta, the ventricle becomes small. In order to become small, all sides of the ventricle and the floor and the ceiling, or chamber, move together. Since the ceiling of the ventricle is the floor of the atrium, the atrium is enlarged when its floor descends. This enlargement causes atrial pressure to become subatmospheric. Therefore, during ventricular contraction, blood is actually sucked back into the atrium from the pulmonary veins and capillaries. This movement of blood from pulmonary veins to left atrium can be identified using Doppler echocardiography.

Finally, after the ventricle is as full as it will get before the next atrial contraction, the heart is in a period of quiescence. During that period, the gradient of pressure between the aorta and the right atrium forces blood through the coronary circulation to deliver O_2 to the myocardium.

Although this sequence of events is described for the left atrium, left ventricle, and aorta, an identical sequence is occurring for the right atrium, right ventricle, and pulmonary trunk, but slightly skewed in time.

An interesting and clinically important asynchronism between left and right ventricular ejection occurs during ventilation. During inspiration, the duration of right ventricular ejection lengthens, while during expiration, it shortens. Since this duration determines when the pulmonic valve closes, during inspiration the pulmonic valve closes tardily. Thus, the second heart sound (S_2) becomes split. Splitting of S_2 during inspiration is termed "physiological splitting." Because in dogs the heart rate accelerates during inspiration and duration of left ventricular ejection shortens, the aortic valve closes early, thus adding to the physiological splitting.

REFERENCES

1. Guyton AC (ed). Textbook of Medical Physiology. 9th ed. Philadelphia, WB Saunders, 1995

2. Berne RM, Levy MN. Cardiovascular Physiology. St. Louis, CV Mosby, 1981
3. Little RC. Physiology of the Heart and Circulation. Chicago, Year Book Medical Publishers, 1985
4. Rusher RF. Cardiovascular Dynamics. Philadelphia, WB Saunders, 1976
5. Burton AC. Physiology and Biophysics of the Circulation. Chicago, Year Book Medical Publishers, 1972
6. Braunwald E, Ross J Jr, Sonnenblick EH. Mechanisms of Contraction of the Normal and Failing Heart. Boston, Little, Brown, 1976
7. Cohn PF. Clinical Cardiovascular Physiology. Philadelphia, WB Saunders, 1985
8. Smith JJ, Kampine JP. Circulatory Physiology: The Essentials. Baltimore, Williams & Wilkins, 1980
9. Katz AM. Physiology of the Heart. New York, Raven Press, 1992
10. Shepherd JT, Vanhoutte PM. The Human Cardiovascular System. New York, Raven Press, 1979
11. Opie LH. The Heart; Physiology and Metabolism. New York, Raven Press, 1991

II

Examination of the Patient with Cardiovascular Disease

4

The History

PHILIP R. FOX

PURPOSE AND IMPORTANCE OF THE MEDICAL HISTORY

Eliciting a good medical history is a technique that must be learned. It requires effort, tact, and patience. Historical information must be analyzed and processed within an organized clinical framework for data analysis.[1–5] History taking is an important art that may be likened to the "glue" binding together subjective aspects of the physical examination and diagnostic tests.[3, 6]

There is a growing and undesirable trend to bypass the time and effort required for an insightful history and thorough examination. It is often simpler to substitute expensive technologic procedures when diagnosis or management could have been readily made with a detailed history and complete examination.[2, 6, 7] An accurate and attentive history is the richest source of information and assists the clinician in evaluating subjective aspects of diagnostic tests.[3, 6–10]

The history and physical examination form the cornerstone of diagnosis.[3, 6, 8] They are crucial for decisions involving clinical evaluation and therapy (Fig. 4–1). A good history should help reveal the system or disease(s) causing clinical signs described by the client's chief complaint. Accordingly, the history collects medical information to (1) help distinguish between cardiac and pulmonary disease, (2) establish a specific diagnosis of heart disease, (3) determine the frequency and extent of associated clinical impairment, (4) assess the response (or lack of response) to therapy, (5) determine the presence of other medical conditions, and (6) establish a doctor-client relationship. The history also provides a sense of pet owner willingness and commitment to treat chronic heart failure, which is usually inexorably progressive.

ELICITING THE HISTORY

Different methods may be used to elicit a medical history,[3, 6–10] but a complete and comprehensive set of well-planned questions is required to obtain necessary information (Table 4–1). During the initial process the owner is asked to relate observations and concerns in his or her own manner. While this may result in many irrelevant facts and is time consuming, it provides a glimpse of the client's intelligence, emotional state, and health care experience. It usually provides important information about the pet's clinical condition, and gives the client the satisfaction of being heard.

The pet owner will not usually volunteer all relevant information without prompting. This is due to incomplete observation of clinical signs, incorrect description of signs through misinterpretation, emotional concern, and a sense of denial that serious illness is present.

The clinician must then direct the client, using a well-planned set of questions designed to evaluate relevant clinical observations. These observa-

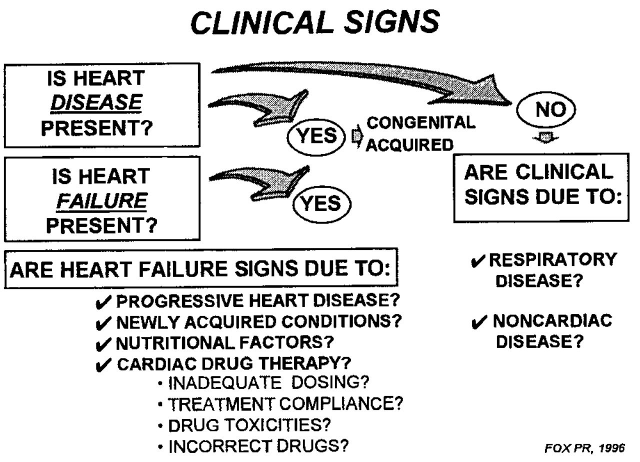


FIGURE 4-1

History algorithm. This highlights basic areas to investigate in order to discern the relationship between clinical signs and cardiac versus noncardiac disease.

tions include (1) determining onset of signs, their related chronology, and severity; (2) uncovering precipitating factors; and (3) assessing response (or lack of response) to therapy. The clinician must elicit a description of all clinical signs, even if the pet owner does not believe them to be relevant. Generally, only those problems deemed most bothersome to the client (the chief complaint) are volunteered.

SIGNALMENT

This part of the objective data base includes the age, breed, and gender. Many diseases have particular breed and gender predilections (chapters 23–25). Acquired cardiorespiratory diseases also have species and breed variation relative to certain diseases.[11–13]

TABLE 4-1
Important Information for the Complete History

Signalment (age, breed, gender)
Geographic origin (pound, breeder, found as stray)
Environment (indoor vs. outdoor)
Diet
Previous medical or surgical problems (include diagnostic procedures and associated results, therapies, outcome)
Preventive health care status (vaccinations, parasites, heartworm prophylaxis)
Chief medical complaint
Date of onset
Acute or gradual
Description of signs (static, regressive, or progressive)
Association of signs with activity
Diagnostic test results if examined elsewhere
Therapies
Doses, duration
Response
General status (weight loss or gain, activity level, appetite, urination and defecation characteristics)

PAST HISTORY

Important clues may be obtained from the pet's past history. For example, congenital heart disorders may be inferred if siblings, dam, or sire have been affected with known cardiovascular disease.[14] Questions concerning the health of related pets should be asked. Also, results from diagnostic procedures, including radiographs, electrocardiograms (ECGs), echocardiograms, and clinical pathology tests performed at other veterinary clinics, are important to evaluate. Frequently, drugs will have been prescribed for known or suspected heart disease. Knowledge of doses, owner compliance, and therapeutic response (or lack of response) can offer valuable insights. In addition, drug toxicities can exert a variety of systemic or metabolic effects and may contribute to clinical signs.

GENERAL HISTORY

A detailed general medical history is important (see Table 4–1).[2–10] Systemic and metabolic disorders may precipitate or cause cardiovascular abnormalities such as hyperthyroidism (chapter 34), chronic renal disease (chapter 35), and a variety of other conditions (chapter 33). Whether the pet's environment is primarily indoor or outdoor may influence its susceptibility to heartworm infection. Previous diet and current diet are important, as certain nutritional deficiencies (e.g., taurine and carnitine deficiency) may cause myocardial dysfunction (chapter 32). Significant past illnesses (e.g., parvovirus infection) or injuries (e.g., traumatic arteriovenous fistula) should be discerned.

SPECIFIC CARDIOVASCULAR HISTORY

SIGNS OF HEART DISEASE

Dyspnea, exercise intolerance, syncope, coughing, and cyanosis are the most common signs of heart disease. Thus, the clinician should be familiar with distinguishing features of respiratory, systemic, and metabolic diseases that cause similar signs (Table 4–2).[2, 8, 10] Cats in heart failure are also usually lethargic and anorectic and tend to hide. They do not cough with pulmonary edema but may with heartworm disease.

Heart failure is a syndrome with variable clinical signs and may be present along with respiratory disease. Therefore, one must distinguish among heart disease, heart failure, and noncardiac diseases relative to clinical signs (see Fig. 4–1) and determine the potential relationship of these disorders to the clinical complaint.

TABLE 4–2
Historical Features Differentiating Cardiac from Respiratory Disease

Clinical Signs or Patient Characteristics	Heart Disease	Respiratory Disease
Small dogs (<20 kg, especially toy and miniature breeds)	Chronic acquired valve disease	COPD; large airway disease
Large/giant breed dogs	Dilated cardiomyopathy	Laryngeal paralysis
Breed-specific predispositions	Congenital heart disorders (chapters 23, 24) Acquired heart diseases DCM (Doberman pinschers; Cocker spaniels) Sick sinus syndrome (miniature schnauzers) Right atrial hemangiosarcoma (German shepherds; Irish setters; Labrador retrievers)	Tracheal stenosis (English bulldogs) Stenotic nares; elongated soft palate; everted laryngeal saccules (brachycephalic breeds) Chronic respiratory infections (Chinese Shar Pei) Ciliary dysfunction (Chinese Shar Pei) Laryngeal paralysis (Bouvier des Flandres)
Body condition	Stunted (severe congenital heart diseases) Cachexia (CAVD; DCM; SBE) Weight loss (hyperthyroidism)	Obese or normal
Cough	With pulmonary edema: mild, grunting, soft Exercise capacity severely decreased between coughing episodes Duration: acute to days	With large airway disease: loud, hacking, brassy, dry, "goose honking," precipitated by excitement Exercise capacity normal between episodes Duration: months to years
Respiratory stridor	No	Upper airway obstruction; nasophryngeal polyps
Exercise capacity	Markedly reduced with left-sided CHF	Large airway disease: generally normal Bronchopneumonia: generally reduced but variable
Syncope	CAVD; HOCM; SAS; DCM; right-to-left cardiac shunting; anemia; pulmonary hypertension; brady- or tachyarrhythmias	Uncommon; may occur in small breed dogs with large airway disease and severe mitral regurgitation
Abdominal distention	Right-sided CHF	No
Peripheral edema	Right-sided CHF	No
Diet	Specific deficiencies (e.g., carnitine; taurine)	No

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DCM, dilated cardiomyopathy; CAVD, chronic acquired valvular disease; MR, mitral regurgitation; TR, tricuspid regurgitation; HOCM, hypertrophic obstructive cardiomyopathy; SAS, subaortic stenosis; SBE, bacterial endocarditis.

Dyspnea

Dyspnea is associated with a large and varied set of conditions:[15, 16] heart failure, respiratory disease, chest wall abnormalities, pleural and pericardial effusions, circulatory disorders, anemia, acidosis, excitement, and pain.

Establishing the degree of activity necessary to provoke dyspnea or its relative onset of action may be helpful.[6] Acute dyspnea suggests pulmonary edema, severe pneumonia, airway obstruction, pneumothorax, or pulmonary thromboembolism. Chronic, progressive dyspnea may occur with right-sided heart failure, pericardial disease, bronchial disease, emphysema, pleural effusions, progressive anemia, or pulmonary neoplasia. Inspiratory dyspnea suggests upper airway obstruction, whereas expiratory dyspnea is typical of lower airway obstruction. Exertional dyspnea implies organic disease (e.g., myocardial failure with dilated cardiomyopathy) or chronic obstructive lung disease. Dyspnea at rest can indicate pneumothorax, pulmonary thromboembolism, or severe congestive heart failure (CHF). Paroxysmal dyspnea may suggest brady- or tachyarrhythmias, especially if accompanied by episodic weakness or syncope. In cats, dyspnea is a common sign of severe thyrotoxicosis.[17]

A history indicating that dyspnea diminished or resolved with diuretics, angiotensin-converting enzyme inhibitors, or digitalis therapy suggests heart failure as an etiology. Response to bronchodilators, antibiotics, or corticosteroids suggests bronchial disease.

Cough

Coughing is associated with a variety of cardiorespiratory conditions, and many coughs sound alike.[6, 15, 18] More than one etiology may coexist. Cardiogenic pulmonary edema in dogs most frequently results from left-sided heart volume overload (mitral regurgitation caused by endocardiosis) or dilated cardiomyopathy. Duration of coughing from acute pulmonary edema is usually less than a week and rapidly progresses in severity. The related cough is generally relatively soft and mild and accompanies exertional dyspnea (in contrast to large airway disease). Chronic pulmonary congestion may cause mild intermittent coughing and nocturnal dyspnea or cough.[19, 20] The predictive value of nocturnal coughing has not been established, however.

When edema is fulminant, the cough may yield small quantities of frothy, pink-tinged foam from the mouth or nares. Acute pulmonary edema may occur without warning and be preceded predominantly by dyspnea.

In dogs, impingement of the left main stem bronchus by a left atrium enlarged by chronic mitral regurgitation contributes to chronic coughing.[20] Cats appear not to cough, however, even when severe left atrial enlargement is present.

Large airway disease in small breed dogs causes chronic paroxysmal coughing characterized as harsh, resonant, dry, and "goose honking" in nature.[19, 20] Coughing may persist for years, is paroxysmal, and is usually elicited by excitement. Less commonly, affected dogs with collars who pull during leash walks will exhibit this coughing. Dogs with collapsed trachea usually have normal exercise capacity between coughing episodes unless congestive heart failure is present, which causes lethargy and weakness.

In cats, pulmonary edema usually results from hypertrophic or restrictive cardiomyopathy. Affected cats do not cough but instead exhibit acute dyspnea, lethargy, and occasionally vomiting.[13]

SYNCOPE

Transient loss of consciousness from inadequate cerebral blood flow defines syncope (chapter 22).[21] It occurs most commonly in coughing, excited, small breed dogs with chronic, severe mitral regurgitation, whose paroxysmal coughing is immediately followed by transient collapse (cough syncope). Syncope or episodic weakness also occurs with other cardiovascular diseases, most notably subaortic stenosis, pulmonary valve stenosis, hypertrophic obstructive cardiomyopathy, pulmonary hypertension, and right-to-left cardiac shunts (tetralogy of Fallot, patent ductus arteriosus). Poor forward cardiac output, as occurs with dilated cardiomyopathy and systemic hypotension from vasodilator drugs, may cause syncope. Tachy- or bradyarrhythmias may also be causative. Complete (third-degree) AV block usually precipitates acute lethargy or collapse.[15]

WEAKNESS AND EXERCISE INTOLERANCE

Although not specific for heart disease, decompensated heart failure is characterized by lack of exercise ability, lethargy, or fatigue. This results from the heart's inability to provide oxygen to satisfy tissue metabolic needs because of myocardial dysfunction, obstruction to ventricular outflow, or arrhythmias.[6, 15] Anemia, systemic and metabolic diseases (e.g., hypoadrenocorticism), drug toxicities (hypotension), and severe respiratory disease may also cause these signs.

OTHER SIGNS OF HEART DISEASE

PARESIS. Acute posterior paresis in cats associated with cardiomyopathy is a characteristic sign of aortic thromboembolism caused by a saddle embolism (chapter 28). Clinical signs[13, 22] include peracute, lateralizing posterior paresis with the distal paw slightly swollen; severe pain manifested by vocalizing; and dyspnea related to congestive heart failure, which often occurs concomitantly with thrombosis. Occasionally, thromboembolism affects a front leg rather than the distal aortic trifurcation. In these cases the right front leg is usually affected.

In dogs, shifting leg lameness has been described as a complication of bacterial endocarditis.[23] Aortic thromboembolism occurs but is rare.[24]

WEIGHT LOSS. Weight loss is a common finding in dogs with chronic, severe heart failure caused by acquired degenerative valve disease or dilated cardiomyopathy (DCM). Cardiac cachexia is associated with gradual but progressive loss of weight despite a relatively normal appetite (chapter 32) and drug therapy. In dogs with DCM, marked weight loss may occur over a short period of 1 to 2 weeks and is sometimes the chief client complaint.

In cats, weight loss is most commonly associated with hyperthyroidism.[17] It reverses when euthyroidism is reestablished (chapter 34). Cats with primary cardiomyopathy do not usually lose weight unless chronic right-sided heart failure is present.

SWOLLEN ABDOMEN OR PERIPHERAL EDEMA. The client may become aware of weight gain manifested by abdominal swelling when ascites is present. Occasionally, severe general retention of extracellular fluid will cause peripheral edema, which is most notable in the extremities. Peripheral edema may also result from hypoproteinemia and obstruction of lymphatics. When edema affects only one leg, local factors such as neoplasia, phlebitis, or neoplasia must be considered.[22]

MUCOUS MEMBRANE COLOR. Clients will occasionally describe abnormal changes in mucous membrane coloration. Cyanosis may be observed in the tongue, gums, or ears of pets with congenital heart diseases causing right-to-left shunting (chapter 24), with congestive heart failure, or with severe respiratory disease. Before cyanosis associated with hypoxemia can be detected, circulation of at least 5 gm/dl of deoxygenated hemoglobin must be present. Pale, gray mucous membranes may result from cyanosis combined with peripheral vasoconstriction. Pink or reddish mucous membrane may be observed during initial stages of septic shock. Injected, dark red mucous membranes may result from cyanosis combined with hypoxemia and re-

duced blood flow.[24] Yellowish discoloration is associated with icterus.

OCULAR AND NEUROLOGIC SIGNS. Systemic hypertension may be heralded by acute blindness with fundoscopic lesions including retinal degeneration, hyphema, and hemorrhage (chapter 35). Occasionally, central nervous system signs, including stupor and coma, may be present.

INTERPRETING THE HISTORY

When eliciting a history, the owner's personality and emotional state must be taken into consideration. It should be appreciated that many owners with severely sick animals may exhibit marked denial of their pets' illness. This is due in part to the increasing importance of the human-animal bond and apprehensions of costs related to veterinary care. Significant historical details should be verified by repeated questions constructed slightly differently. A friend or family member who brings the pet in for examination may not have actually observed the pet's clinical signs, and this must be ascertained.

REFERENCES

1. Dimsdale JE. Delays and slips in medical diagnosis. Perspect Biol Med 27:213, 1984
2. Abrams J. Essentials of Cardiac Physical Diagnosis. Philadelphia, Lea and Febiger, 1987
3. Sapira JD. The history. *In* The Art and Science of Bedside Diagnosis: Baltimore, Urban Schwartzenberg, 1990, p 9
4. Osborne CA. Diagnosis by rule-out: Judgment in the absence of certainty. *In* Bonagura JD (ed): Kirk's Current Veterinary Therapy. Vol XII. Philadelphia, WB Saunders, 1995, p 7
5. Lund EM, Klausner JS. Clinical epidemiology for the veterinary practitioner: The diagnostic process. *In* Bonagura JD (ed): Kirk's Current Veterinary Therapy. Vol XII. Philadelphia, WB Saunders, 1995, p 7
6. Braunwald D. The history. *In* Braunwald E (ed): Heart Disease. 4th ed. Philadelphia, WB Saunders, 1992, p 12
7. Thibault GE. The appropriate degree of diagnostic certainty. N Engl J Med 331:1216, 1994
8. Hurst JW, Morris DC, Crawled IS, et al. The history: Symptoms and past events related to cardiovascular disease. *In* Hurst JW, Schlant RC, Rackley CR, et al (eds): The Heart: Arteries and Veins. 7th ed. New York, McGraw-Hill, 1990, p 122
9. Jones D. History and physical examination. *In* Birchard SJ, Sherding RG (eds): Saunders Manual of Small Animal Practice. Philadelphia, WB Saunders, 1994, p 1
10. Schaer M. The medical history, physical examination, and physical restraint. *In* Sherding RG (ed): The Cat. Diseases and Clinical Management. New York, Churchill Livingstone, 1994, p 7
11. Dhein CR, Prieur DJ, Riggs MW, et al. Suspected ciliary dysfunction in Chinese Shar Pei pups with pneumonia. Am J Vet Res 51:439, 1990
12. Greenfield CL. Canine laryngeal paralysis. Comp Cont Ed 9:1011, 1987
13. Fox PR. Feline myocardial diseases. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 435
14. Patterson DF. Epidemiologic and genetic studies of congenital heart disease in the dog. Circ Res 23:171, 1968
15. Ware WA. The cardiovascular examination. *In* Nelson RW, Couto CG (eds): Essentials of Small Animal Internal Medicine. St Louis, Mosby–Year Book, 1992, p 3
16. Turnwald GH. Dyspnea and tachypnea. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 64
17. Broussard LD, Peterson ME, Fox PR. Changes in the clinical and laboratory findings in hyperthyroid cats for 1982–1992. J Am Vet Med Assoc 302:302, 1995
18. Ettinger SJ, Barret KA. Coughing. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 57
19. Hamlin RL. Is a cough due to heart disease or lung disease? Vet Forum, May, 1994, p 59
20. Hamlin RL. Identifying the cardiovascular and pulmonary diseases that affect older dogs. Vet Med, May, 1990, p 483
21. Kapoor WN. Hypotension and syncope. *In* Braunwald E (ed): Heart Disease. 4th ed. Philadelphia, WB Saunders, 1992, p 875
22. Suter PR, Fox PR. Peripheral vascular diseases. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1994, p 1068
23. Calvert CA. Endocarditis and bacteremia. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 419
24. Schertel ER, Muir WW. Shock: Pathophysiology, monitoring and therapy. *In* Kirk RW (ed): Current Veterinary Therapy. Vol X. Philadelphia, WB Saunders, 1989, p 316

5

The Physical Examination

D. DAVID SISSON
STEPHEN J. ETTINGER

Information from the physical examination, combined with that obtained from a complete history, comprises the foundation for diagnosis, initial treatment, and evaluating response to therapy. Despite major technologic advances in cardiology, the history and physical examination remain the most important components of the cardiac evaluation. The tools employed are the five senses, supplemented at times by instruments designed to augment their sensitivity, such as the stethoscope or ophthalmoscope. Although a complete physical examination should be performed on each patient, practical considerations often dictate the amount of time and effort devoted to a particular organ system. Table 5–1 identifies dependable signs of cardiovascular disease in the dog and cat. Note that 8 of the 12 signatures of cardiovascular disease are based on the physical examination.[1]

A thorough written record of the entire cardiac examination is essential to follow medical progress. Preprinted forms requiring simple check-marks or symbols provide the essential information for subsequent follow-up and review.

INSPECTION

BREATHING

Initially, the clinician should observe each patient from a distance, noting the breed, general body condition, attitude, temperament, conformation, and ability to ambulate. The rate and character of respiration are observed, and apparent effort required to breath is assessed. *Tachypnea* accompanied by cough, increased effort, or altered pattern of respiration is a frequent manifestation of heart failure or respiratory disease. Rapid, shallow breathing is often observed in anxious pets at the time of the examination. Animals with true *dyspnea* often stand with their elbows abducted in an attempt to improve ventilation. More severe respiratory distress is evidenced by extension of the head and neck and by open-mouth breathing (Fig. 5–1). *Orthopnea* is demonstrated when a severely compromised patient sits on its haunches and refuses to assume a recumbent position. This finding is common in animals with respiratory distress caused by severe pulmonary edema, pleural effusion, bronchopneumonia, pneumothorax, or acute diaphragmatic hernia. Pet owners often report that their animal has been restless at night, with difficulty sleeping.

EXERCISE INTOLERANCE

Animals with heart disease are often reluctant to exercise or unable to perform to expected standards. With severe disease, they may be too

TABLE 5–1
Dependable Signs of Cardiovascular Disease in the Dog and Cat

1. Grade IV/VI or louder systolic murmurs
2. Grade III/VI systolic murmurs in the absence of anemia
3. Diastolic murmurs of any intensity
4. Gallop heart sounds (an accentuated third, fourth, or summation sound)
5. Palpable precordial thrills
6. Peripheral cutaneous thrills
7. Generalized venous engorgement
8. Localized absence of arterial pulsations
9. Radiographic or echocardiographic evidence of cardiac enlargement
10. Left bundle branch block (ECG)
11. Right ventricular enlargement criteria (ECG)
12. Certain cardiac arrhythmias (atrial fibrillation or flutter; persistent or frequent premature atrial or ventricular contractions; paroxysmal tachycardia; high-grade atrioventricular block)

Modified from Detweiler DK, Patterson DF, Luginbühil H, et al. Diseases of the cardiovascular system. *In* Catcott EJ (ed): Canine Medicine. Santa Barbara, California, American Veterinary Publishers, Inc. 1968.

weak to ambulate more than a few yards. Subtle degrees of exercise intolerance are difficult to recognize or to quantify, particularly in cats and nonworking dogs. In this regard, the owners' observations, as elicited in the history, must be relied upon. Classes of heart failure, analogous to those developed by the New York Heart Association for humans and based largely on ability to exercise, have been adopted for categorizing heart disease severity in dogs (see Appendix). Such classifications are relatively useless for categorizing cats with heart disease. Often, the only observed change in cats with developing heart failure is a tendency toward more reclusive behavior.

WEIGHT LOSS

Chronic heart failure may cause severe weight loss, referred to as *cardiac cachexia.* It is distinguished from other forms of weight loss in that affected animals suffer a substantial loss of lean body mass.[2] Muscle wasting is often particularly noticeable in the temporal region of the head and along the dorsal lumbar area (Fig. 5–2). Such findings are particularly common in dogs with dilated cardiomyopathy, severe heartworm infestation, or chronic degenerative valvular disease. Pathophysiology of cardiac cachexia is complex, but causes include decreased appetite, malabsorption, gastrointestinal protein loss, and increased production of tumor necrosis factor and various cytokines (chapter 32).

ASCITES

Abdominal distention due to ascites is common in dogs with pericardial disease or right-sided heart failure. Common causes of right-sided heart failure in dogs include heartworms, dilated cardiomyopathy, congenital or acquired tricuspid valve insufficiency, and pulmonic stenosis. In cats with congestive heart failure, ascites occurs less commonly and is usually less pronounced. To the untrained observer, patients with ascites may appear obese owing to abdominal distention. The distinction is usually easily made by careful palpation and ballottement, but abdominocentesis is sometimes required to confirm ascites in obese patients.

DISTENDED JUGULAR VEINS

Animals with right-sided heart failure or pericardial disease typically manifest jugular venous distention (Fig. 5–3). Jugular pulses are abnormal.

PERIPHERAL EDEMA

Swollen extremities and ventral edema are uncommon with congestive heart failure. When present, the edema is usually symmetric in distribution and virtually always indicates severe right-sided heart failure.

EXAMINATION OF THE HEAD AND NECK

EVALUATION OF THE SKIN AND MUCOUS MEMBRANES

The mucous membranes are normally moist and pink. A variety of disorders alter the appearance of the

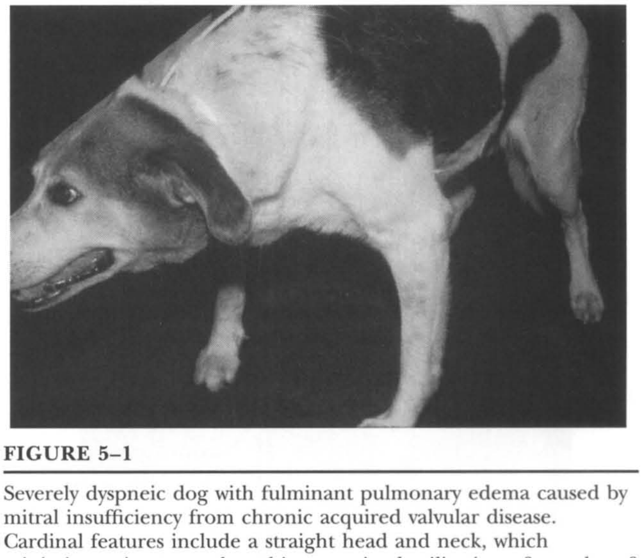


FIGURE 5–1

Severely dyspneic dog with fulminant pulmonary edema caused by mitral insufficiency from chronic acquired valvular disease. Cardinal features include a straight head and neck, which minimize resistance to breathing; maximal utilization of muscles of respiration, evidenced by abducted elbows; and open-mouth breathing. Notice the commissures of the mouth, which are drawn back, and a glaring stare, associated with anxiety and dyspnea. (Courtesy of Dr. Philip Fox, The Animal Medical Center.)

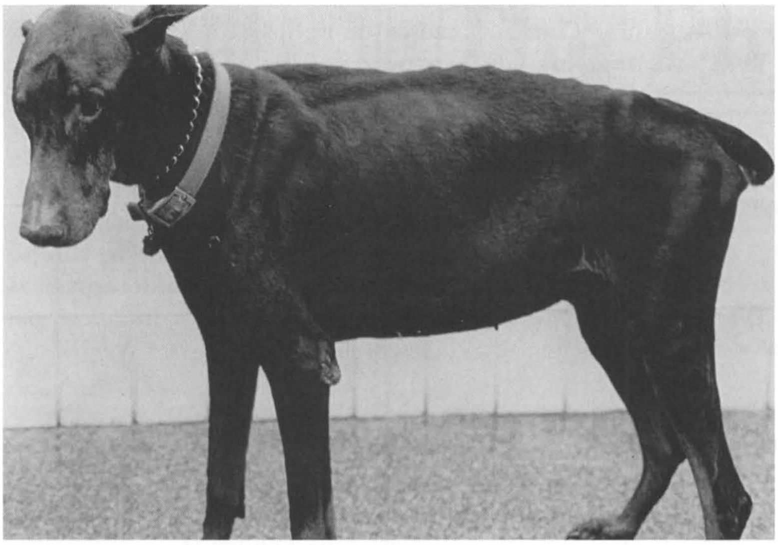


FIGURE 5–2

Cardiac cachexia, evidenced by generalized muscle wasting, is apparent in this Doberman pinscher with chronic congestive heart failure caused by dilated cardiomyopathy.

mucous membranes; some reflect primary cardiac or circulatory disorders whereas others indicate responses of the circulatory system to systemic disease or environmental challenges. Thus, while anemia and polycythemia are characterized by pale or injected mucous membranes, respectively, such findings are a very insensitive and unreliable way to estimate the circulating mass of red blood cells. The mucous membranes often appear pale in nervous animals, especially cats, and they sometimes appear injected in otherwise normal patients. Animals suffering from shock or hypothermia often have pale, ashen mucous membranes. In these circumstances, capillary refill time, normally 1 or 2 seconds long, is also often noticeably prolonged as a result of reduced cardiac output. In the majority of dogs and cats presented in heart failure, mucous membrane color and capillary refill times are normal, emphasizing the fact that such assessments serve only to distinguish animals with particularly severe disease.

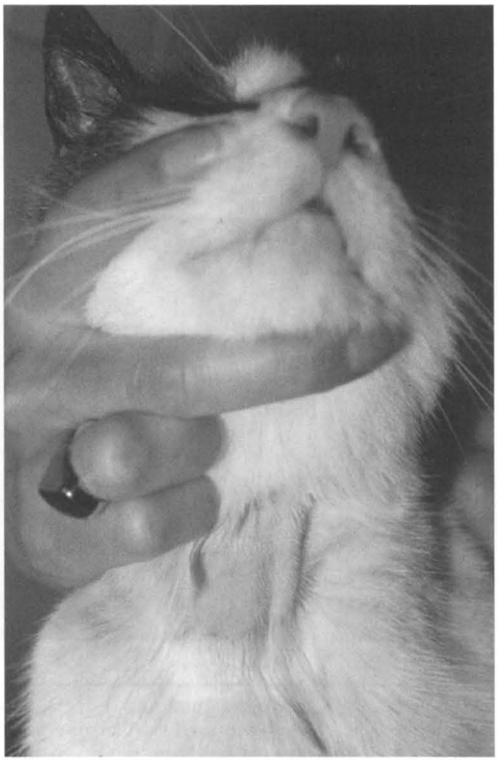


FIGURE 5–3

Jugular venous distention is apparent in this cat with severe right-sided congestive heart failure. (Courtesy of Dr. Philip Fox, The Animal Medical Center.)

Cyanosis is defined as bluish discoloration of the mucous membranes or the skin (Color Plate 1). The magnitude of cyanosis is determined by the concentration of reduced hemoglobin in the blood perfusing the regional capillaries. Cyanosis is usually observed only when the concentration of deoxygenated hemoglobin exceeds 5 g/dl.[3] It is important to distinguish patients with *central cyanosis* from those with *peripheral cyanosis.*

Central cyanosis indicates that cyanosis is generalized, involving all body tissues, including skin mucous membranes. It results from arterial hypoxemia or increased concentrations of abnormal hemoglobin pigments such as methemoglobin. Mechanisms of arterial hypoxemia include (1) inspiring air with an abnormally low oxygen concentration, (2) hypoventillation, (3) diffusion impairment, (4) ventilation-perfusion mismatch, or (5) shunting unoxygenated blood from the right side of the circulation to the left. Pulmonary edema due to left-sided heart failure results in arterial hypoxemia and central cyanosis, mainly as a result of ventilation-perfusion mismatching. Anatomic shunts resulting in central cyanosis are usually caused by congenital cardiovascular malformations such as tetralogy of Fallot, Eisenmenger's syndrome, and right-to-left–shunting patent ductus arteriosus (PDA). The latter is characterized by "differential cyanosis," in which the caudal half of the body is cyanotic while the head and front legs receive blood with near-normal oxygen

saturation. The careful examiner compares and contrasts the appearance of oral and conjunctival mucous membranes with those of the vulva or penis and prepuce. Arterial blood gas analysis confirms the presence and elucidates the cause of arterial hypoxemia.

Peripheral cyanosis is usually observed in the distal extremities, such as the digits and ear tips. By definition, arterial oxygen saturation is normal in patients with peripheral cyanosis, but a larger proportion of the oxygen is extracted from the capillary and venous blood perfusing the affected region. Peripheral cyanosis results from decreased arterial blood flow or venous pooling and, thus, may develop secondary to reduced cardiac output, regional vasoconstriction, or vascular obstruction. Shock and hypothermia are common causes of peripheral cyanosis. Regional cyanosis of the digits, nailbeds, and footpads is a well-known physical finding in cats with aortic thromboembolism.

Other abnormalities of the skin and mucous membranes are less likely to indicate or be associated with cardiovascular disease. Icterus, manifested as a yellow or orange cast to the mucous membranes and sclera, signifies elevated total serum bilirubin. Causes include obstruction to bile flow, a variety of hepatopathies, or increased rate of red blood cell destruction. Jaundice is a most unusual finding with heart disease, occurring most commonly in heartworm-infected dogs with vena caval syndrome. Ecchymotic hemorrhages in the skin or mucous membranes occur with severe polycythemia but are more typical of a systemic vasculitis or coagulopathy. Petechiae are observed most commonly with thrombocytopenia but are occasionally noted with infective endocarditis.

THE OCULAR EXAMINATION

Certain cardiovascular diseases cause marked ocular changes. Careful evaluation of the eyes, including a careful fundic examination, is therefore important. In cats with systemic hypertension, diminished or absent pupillary responses are common due to retinal detachment or retinal hemorrhages (Color Plate 2).[4] Papilledema, swelling of the optic disc, is also common in this circumstance. Retinal hemorrhages are also observed with polycythemia or bacterial endocarditis. Central retinal degeneration is reported in about one third of cats with dilated cardiomyopathy caused by taurine deficiency.[5] It is characterized by horizontally linear, hyperreflective areas that can expand to incorporate most of the fundic region.

EXAMINATION OF THE JUGULAR AND OTHER SUPERFICIAL VEINS

Two principal observations can be made from examination of the jugular veins: (1) the level of venous pressure, and (2) the type of venous wave pattern. The jugular veins are not normally distended and should empty quickly following manual compression at the thoracic inlet. Normal venous pulsations do not usually extend higher than one third of the way up the neck in healthy, erect-standing animals. During inspiration, jugular venous pressure normally declines, causing the vein to collapse, but the amplitude of the pulse waves increases slightly owing to increased venous return.

The jugular venous pulse pattern reflects events of the cardiac cycle (Fig. 5–4).[6] This pattern is often discernible in large-breed dogs with slow heart rates, but it is often camouflaged in small dogs or cats with rapid heart rates. The wave that results from atrial systole is called the "a" wave. The "x-descent" immediately follows the "a" wave and results from atrial relaxation. A small "c" wave is often present and occurs simultaneously with the carotid arterial pulse but results primarily from tricuspid valve closure. The "x′-descent" that follows results from downward movement of the tricuspid annulus as the ventricles start to contract at the onset of systole. Filling of the right atrium during late ventricular systole results in the "v" wave; this is followed by the "y-descent" as right atrial pressure falls when the tricuspid valve opens.

Distention of the jugular veins reflects elevated systemic venous pressure and occurs with right-sided heart failure (systolic or diastolic), pericardial disease, hypervolemia, or obstruction of the superior vena cava (Fig. 5–3). Common acquired heart diseases resulting in systemic venous hypertension include pericardial effusion with cardiac tamponade, heartworm disease, cardiomyopathy, and tricuspid valve insufficiency due to valvular degeneration or pulmonary hypertension. Some of the congenital heart defects causing increased jugular venous pressure include pulmonic stenosis, tricuspid valve dysplasia, cor triatriatum, and pericardial cysts. Abnormally distended jugular veins should alert the examiner that right-sided heart failure or any of

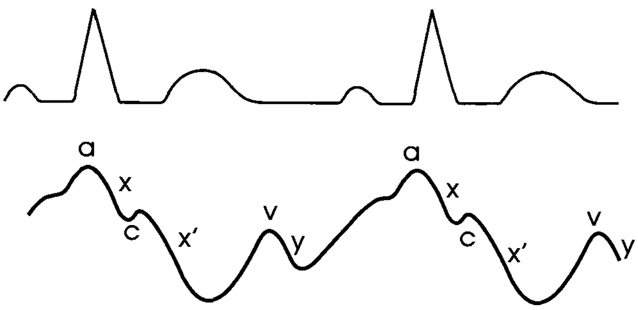


FIGURE 5–4

The normal pattern of jugular venous pulses resulting from hemodynamic events in the right heart. The "a" wave results from atrial systole, the "x descent" from atrial relaxation, the "c" wave from tricuspid valve closure, and the "v" wave from atrial filling. The "y descent" is inscribed when the tricuspid valve opens and the right atrium empties.

the aforementioned cardiovascular disorders may be present.

In addition, the pattern of venous pulsations may provide clues to the etiology of the disorder. Abnormally prominent "a" waves are observed when the right atrium contracts against a hypertrophied, noncompliant, or restricted right ventricle. Intermittent, bounding jugular venous pulsations occur when disturbances of the cardiac rhythm cause the right atrium to contract against a closed atrioventricular valve, forcing the blood to move retrograde into the jugular veins. These giant, or *cannon*, "a" waves are most commonly observed in dogs with complete heart block. Prominent "v" or "cv" waves (fusion of "c" and "v" waves in the absence of an "x-descent") are seen with tricuspid insufficiency. The accentuated jugular pulses observed in animals with pericardial disease result from abnormal "x" and "y" descents. A jugular pulse should be differentiated from pounding of the carotid artery in nervous animals.

PALPATION OF THE NECK

Careful neck palpation can identify enlarged thyroid glands, particularly in cats with hyperthyroidism. The ability to "slip" an enlarged thyroid gland is particularly helpful in aged cats with a heart murmur or gallop heart sounds. Palpation of a mass and the presence of a thrill or bruit near the larynx of an aged dog is highly suggestive of a thyroid carcinoma and associated arteriovenous fistula. Thyroid function is usually normal or depressed in affected dogs, but high-output heart failure may develop from the many arteriovenous communications developing in association with this tumor. Dilation of the esophagus in young dogs with a history of regurgitation suggests congenital megaesophagus or a vascular ring anomaly. The external jugular veins are distended and noncompressible when obstructed by thromboemboli. Such obstructions may develop as a sequela to intravenous catheterization or compression of the cranial vena cava by a mediastinal mass. Cranial vena caval obstructions also cause head and neck edema and pleural effusion. Lymph nodes, laryngeal masses, and tracheal malformations or collapse can also be palpated.

EXAMINATION OF THE ABDOMEN

Abdominal ballottement and palpation are performed to determine the presence of ascites and hepatomegaly. These findings are expected with advanced disorders of the right-side of the heart, the pericardium, and obstructive lesions of the posterior vena cava. Although splenomegaly may also be present in heart failure, it is not usually a striking finding. The term *hepatojugular reflux* refers to distention of the jugular veins elicited by compression of the abdomen for 10 to 30 seconds.[7] This abnormal finding is associated with elevated central venous pressure and inability of the right side of the heart to accommodate any additional venous return. Careful abdominal palpation may also reveal masses associated with hemorrhage and abdominal effusion or small irregular kidneys compatible with renal failure and arterial hypertension.

EXAMINATION OF THE THORAX

Examination of the thorax commences with inspection and palpation for obvious deformities of the ribs (flail chest), sternum (pectus excavatum, pectus carinatum), and the thoracic spine (kyphoscoliosis). Respirations and their frequency, regularity, and depth, as well as the effort required during inspiration and expiration, should be noted. The chest should be palpated, and the location and intensity of the *cardiac impulse*, commonly referred to as the apex beat, should be noted. This region is also the *point of maximal intensity* of the heart sounds in the normal animal. The apex beat may be displaced by any condition that alters the position of the heart within the chest cavity, e.g., intrathoracic neoplasms, diaphragmatic hernia, pleural effusions, or cardiomegaly. In these circumstances, or with obese patients, the apex beat may be reduced in intensity or absent. The presence and location of a palpable *thrill* (vibrations) should be noted, which identifies the point of maximal intensity of a loud heart murmur.

Percussion, although of some value in large animals for the assessment of heart size, is much less reliable in the dog and cat. The use of percussion is of greater value in the detection of pneumothorax in which the lungs sound hyperresonant, or pleural effusion, in which the lungs are hyporesonant.

PRINCIPLES OF THORACIC AUSCULTATION

Auscultation is the most valuable part of the cardiovascular examination, providing essential information about the heart and great vessels and allowing evaluation of the airways and pulmonary parenchyma. The importance of auscultation cannot be overemphasized.

Too often the clinician advances to sophisticated diagnostic procedures, bypassing the basic steps of the physical examination, thereby missing significant clinical information relevant to the diagnosis and treatment.

THE MODERN STETHOSCOPE

Auscultation is accomplished with the binaural stethoscope first introduced by George Cammann in 1855.[8] Stethoscopes vary in quality of design and of sound transmission. Imperfections in the tubing or chest piece, or wax lodged in the ear tips, may interfere with normal sound conduction.

The best instrument is the one that fits the ear canals comfortably and transmits both normal and abnormal heart and lung sounds clearly. A good stethoscope should have comfortable ear pieces angled slightly forward to fit snugly into the ear canals. Most come with both soft and firm ear pieces to assure a comfortable fit. In theory, double tubing is superior to single tubing in transmitting sounds accurately, especially at higher frequencies. In practice, both single tubing (Littmann-type) and double tubing (Rappaport-Sprague–type) models seem to work well. The best tubing is about 1/8 inch (3 mm) in internal diameter and should be as short as practical, typically 14 to 18 inches, for easy use. The chest piece should permit accentuation of either high- or low-frequency vibrations. In most models this is accomplished by a bell and diaphragm, a design we favor. When the bell is placed gently on the thorax, it accentuates lower-frequency heart sounds (such as S_3 and S_4) and attenuates higher-frequency sounds. If the bell is held too firmly on the chest, the underlying skin acts as a diaphragm, negating the low-frequency attributes of the bell. When the diaphragm of the chest piece is placed firmly on the thorax, it transmits a wider band of frequencies than the bell. The diaphragm tends to attenuate low-frequency sounds and to accentuate higher-frequency sounds (such as S_1 and S_2). Diaphragms vary from small pediatric to large adult sizes. A large diaphragm is more sensitive, as it gathers sounds from a wide area, but a small diaphragm has the advantage of permitting better sound localization in a small dog or cat.

PSYCHOACOUSTICS

Figure 5–5 indicates the range of frequencies within which heart sounds and murmurs occur in contrast to normal human speech.[9] The human ear does not hear all sounds of equal intensity with equal ease, and the threshold of audibility differs from person to person depending upon individual hearing ability.[8, 9] Higher volume is required for low-frequency sound to be heard. For example, a sound at 32 cycles per second (Hz) requires 100 times the intensity to make it as audible to the normal human ear as a sound transmitted with a frequency of 256 Hz.

A quiet environment is required for successful auscultation. The smallest interval that can be discriminated by the human ear is 20 milliseconds.[10] When a louder sound precedes a softer sound, the latter may not be detected, a phenomenon known as fatigue. Even low-intensity background noise can obscure much of the sound, a phenomenon known as masking.[11]

Purring sounds and harsh respiratory noises also disrupt normal heart sound recognition and may mimic murmurs. Holding the animal's nares closed or gently brushing a small cotton pledget with alcohol

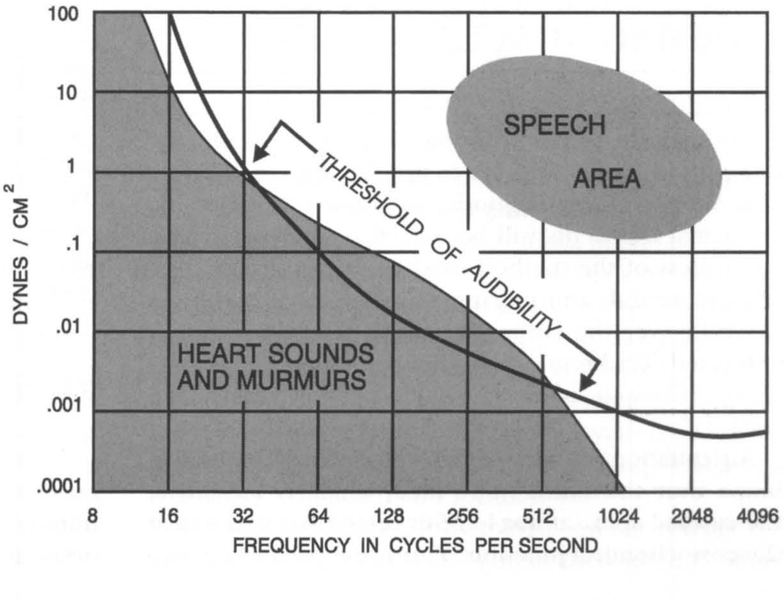


FIGURE 5–5

Only a small segment of the total vibratory energy of a cardiac murmur is audible because of the intrinsic limitations of the human ear. Low-frequency heart sounds are particularly difficult to hear. (From Butterworth JS, et al. Cardiac Auscultation. New York, Grune & Stratton, 1960.)

against the nasal region may limit such sounds. Purring often can be discouraged by turning on a faucet near the cat, pressing on the larynx, or by other physical maneuvers.

ELECTRONIC STETHOSCOPES

Most of the currently available electrical amplifying stethoscopes amplify both the heart sounds and external background noise. Except for the hearing impaired, they offer no substantial advantage over the traditional stethoscope. However, technology now exists to accentuate or attenuate particular band frequencies.[8] Frequency shifting is also possible, permitting the detection of diagnostically important audible sounds. With these techniques it is possible to compensate for selective hearing loss. It is also possible to eliminate distractive sounds by using an appropriate bandpass filter. As these and other methods of sound processing and display are developed, electronic stethoscopes may become more practical in the future.

PHONOCARDIOGRAPHY

A permanent, written recording of the heart sounds is provided by a phonocardiogram.[12] An electrocardiogram (ECG) is usually recorded simultaneously with the heart sounds for timing (Fig. 5–6). Modern phonocardiographs accomplish electronic filtering of the heart sounds in a variety of ways so that a relatively narrow band of sounds can be recorded. Voltage limitation is provided to enable simultaneous display of soft diastolic murmurs and loud systolic murmurs. Arterial pressures, respiration, M-mode ultrasound, or other physiologic parameters may be concurrently recorded if available.

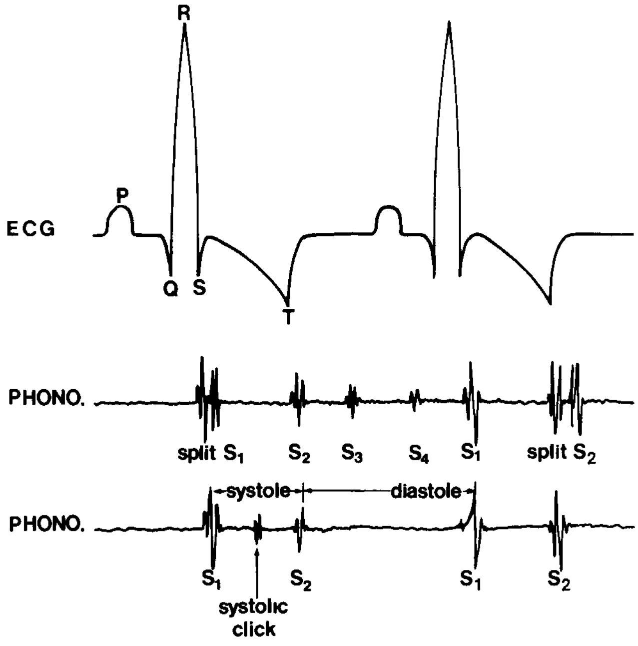


FIGURE 5–6

Illustrations of relationships between the electrocardiogram *(ECG)* and timing of heart sounds. Electrical activity depicted on the ECG precedes cardiac mechanical activity shown by the phonocardiogram *(phono)*. The QRS complex represents ventricular activation. The atrioventricular valves close as the ventricles eject blood through the semilunar valves, and the first heart sound *(S_1)* occurs at the R-wave downstroke. The second heart sound *(S_2)* occurs at the end of ventricular contraction (i.e., ventricular systole), when the semilunar valves close. The third heart sound *(S_3)* occurs during the first half of diastole during passive ventricular filling (e.g., between the T wave and ensuing P wave). The fourth heart sound *(S_4)* occurs late in diastole following atrial activation (P wave) and contraction. (From Gompf RE. The clinical approach to heart disease: History and physical examination. *In* Fox PR (ed): Canine and Feline Cardiology. 1st ed. New York, Churchill Livingstone, 1988, p 29.)

CARDIAC AUSCULTATION

Thoracic auscultation should be performed in a systematic fashion.[13, 14] Failure to use this approach invariably results in misdiagnosis, as some murmurs and abnormal transients will be missed or misinterpreted. Regardless of the method used to define the location of heart sounds and murmurs, it is important to listen carefully over the entire thorax when heart disease is suspected. Traditional areas of auscultation include the mitral, tricuspid, aortic, and pulmonic valve areas (Fig. 5–7).[12–14]

Auscultation usually begins by placing the stethoscope over the mitral valve area, which is located at the cardiac apex, at the left 5th intercostal space near the costochondral junction. This is the *point of maximal intensity* of the heart sounds in the normal animal. By advancing the stethoscope cranially along the left sternal border to the 3rd to 4th intercostal spaces, the region of the pulmonic valve area is auscultated. The aortic valve area lies dorsal and slightly caudal to the pulmonic valve area in the middle third of the left thorax at the 4th intercostal space. In the smaller dog and in most cats, the pulmonic and aortic regions overlap, making their separation difficult. Sounds transmitted from the tricuspid valve area are best heard from the 3rd to 5th intercostal spaces at the junction of the lower and middle thirds of the right thorax.

REVISED AREAS OF AUSCULTATION

Instruction in the technique of cardiac auscultation can be greatly facilitated by redefinition of the traditional areas of cardiac auscultation, emphasizing the origin and transmission of both normal and abnormal

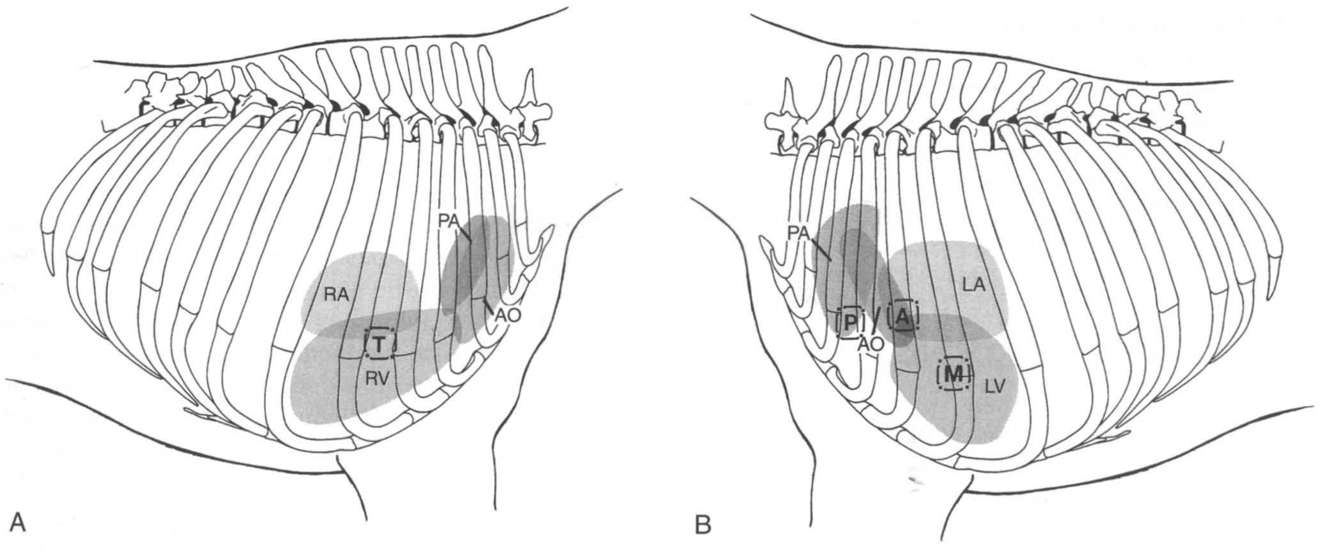


FIGURE 5–7

Areas of cardiac auscultation. Traditional areas include the tricuspid *(T)* valve area on the right hemithorax (A), and the mitral *(M)*, aortic *(A)*, and pulmonic *(P)* valve areas on the left hemithorax (B). The shaded regions represent newly revised areas for auscultation. (A) On the right hemithorax, the *PA* (pulmonic area) and *AO* (aortic area) are also represented, together with the right atrial *(RA)* and right ventricular *(RV)* areas. (B) On the left hemithorax, four landmark areas are identified: *LA*, left atrial area; *LV*, left ventricular area; *AO* (aortic) and *PA* (pulmonic) areas.

heart sounds (Fig. 5–7).[15] In this revised scheme, the aortic area consists of the traditional aortic valve area on the left side of the thorax but also includes another area on the right cranial thorax, reflecting the fact that murmurs arising from aortic valve abnormalities are often heard in both locations. For example, the murmur of aortic stenosis is often louder on the right hemithorax than at the left side of the heart base.[14] The murmur of aortic insufficiency is usually best heard in the traditional aortic area on the left, as is the aortic component of the second heart sound. The left ventricular area is centered just ventral to the traditional mitral area at the cardiac apex. Gallop sounds generated in the left side of the heart are best heard in this location.[15] This is also a good location to hear the murmurs of mitral stenosis, mitral regurgitation, and aortic regurgitation. The left atrial area lies dorsal to the left ventricular area, and here the murmur of mitral regurgitation is often heard best. The revised pulmonic area consists of the traditional pulmonic valve area on the left side of the thorax but also includes a corresponding area on the right cranial thorax. The murmurs of pulmonic stenosis and pulmonic insufficiency are usually best heard in the pulmonic area on the left, as is the pulmonic component of the second heart sound. The right ventricular area occupies the area traditionally identified as the tricuspid valve area. The murmurs of tricuspid stenosis and ventricular septal defects are usually heard best in the right ventricular area, as are gallop heart sounds generated in the right side of the heart. The right atrial area, defined as the region dorsal to the right ventricular area, is where the murmur of tricuspid regurgitation is best heard.

Using a simpler approach, the location of all murmurs may be described as occurring at the left heart base (including the aortic and pulmonic regions), the left apex (mitral region), or the right apex (tricuspid region). Although simpler, this approach places less emphasis on the genesis of murmurs and transient heart sounds than do other methods, and it is less valuable for teaching auscultation.

NORMAL AND ABNORMAL TRANSIENT HEART SOUNDS

CLASSIFICATION OF HEART SOUNDS

Cardiovascular sounds of relatively short duration are referred to as *transient heart sounds*.[13, 15, 16] These include the two normal heart sounds, S_1 and S_2, systolic ejection sounds, mid to late systolic clicks, early diastolic sounds (pericardial *knocks*, tumor *plops*, and opening *snaps*), and accentuated S_3 and S_4 heart sounds (Fig. 5–6).[14, 15, 17] Murmurs constitute groups of sound vibrations of longer duration arising from the heart or great vessels and possess a variety of distinguishing characteristics: intensity, timing, radiation, frequency, character, and location.

A review of normal physiologic events reveals the genesis of heart sounds and guides their identification.

Other heart sounds are recognized by reference to the prominent first two normal heart sounds (S_1 and S_2) auscultated as *lub-dub,* in relationship to the palpated peripheral pulse. Most heart sounds may be adequately characterized by a description of their frequency or pitch, the time of their occurrence in the cardiac cycle, and the location on the chest wall where they are best heard.

THE FIRST HEART SOUND (S_1)

S_1 occurs at the onset of ventricular systole (Fig. 5–6) and is associated with a palpable apex beat just prior to the rise in arterial pressure; S_1 is louder, longer, and lower pitched than the second heart sound.[14] The major audible portion of S_1 is associated with closure of the mitral and tricuspid valves, and it is heard best at the mitral and tricuspid valve areas. The sound is not generated by the valve cusps slapping shut but rather by the sudden acceleration and deceleration of blood and tensing of the valve cusps, chordae tendineae, and related structures.[17] Other elements that contribute to S_1 are vibrations due to early ventricular muscle contraction, opening of the semilunar valves at the end of isovolumic contraction, and vibrations related to rapid early acceleration of blood in the ventricles.

In the dog, S_1 is approximately 80 msec in duration and begins approximately 20 msec after the onset of ventricular depolarization, near the beginning of the QRS complex.[12, 14] Time relationships in the cat are similar but slightly shorter in duration.

The first heart sound is loudest in young, thin animals and in those with high sympathetic tone, tachycardia, systemic hypertension, or anemia. Dogs with acquired valvular disease causing mitral insufficiency also have S_1 with increased intensity.

A first heart sound of diminished intensity may be auscultated in obese dogs or cats; S_1 is also decreased in animals with pleural or pericardial effusion, diaphragmatic hernia, emphysema, shock, decreased myocardial contractility (dilated cardiomyopathy), or prolonged P-R intervals.

SPLIT S_1. Occasionally, the first sound is split into two components due to asynchronous closure of the A-V valves or accentuation of the later ejection components of the first heart sound (Fig. 5–6). Splitting can occasionally be appreciated at the cardiac apex and mitral valve region in healthy, large-breed dogs.[14] It may be attributed to electrical disturbances (bundle branch block, ectopic beats, or cardiac pacing) or to mechanical factors (mitral or tricuspid stenosis).[12, 14] All these conditions delay either mitral or tricuspid valve closure and produce asynchronous valve closure. A split first heart sound must be distinguished from a presystolic gallop, ejection sounds, and systolic clicks.

EJECTION SOUNDS

Ejection sounds are high-frequency sounds occurring early in systole in association with hypertension, dilatation of the great vessels, or the opening of abnormal yet mobile semilunar valves. These sounds are best appreciated at the left heart base in the aortic or pulmonic areas. Ejection sounds are occasionally reported in animals with congenital heart diseases such as tetralogy of Fallot, aortic stenosis, and pulmonic stenosis, and acquired diseases such as heartworm disease. More often, ejection sounds are recognized on the phonocardiogram only and not by auscultation.

SYSTOLIC CLICKS

Systolic clicks are short, mid- to high-frequency sounds that typically occur in mid or late systole (Fig. 5–6). They are best heard over the mitral or tricuspid valves; may vary in occurrence, timing, and intensity; occur most commonly in dogs with early degenerative valvular disease; and are often accompanied by a systolic murmur of mitral regurgitation.[12, 14] In people, systolic clicks are most often due to systolic A-V valve leaflet prolapse.[16] Their origin in dogs is uncertain, but they are likely caused by tensing of redundant valve leaflets or elongated chordae tendineae. They may be misinterpreted as gallop sounds, which also produce a triple cadence on auscultation. Systolic clicks can be easily distinguished from gallop sounds by noting that they are high-frequency sounds best heard between S_1 and S_2 using the stethoscope diaphragm.

THE SECOND HEART SOUND (S_2)

This sound is of higher frequency and shorter duration (60 msec in dogs) than the first sound, and it is heard best at the aortic and pulmonic valve areas (Fig. 5–7).[12, 14] Vibrations contributing to S_2 are produced by early muscular relaxation, blood vibration in the great vessels, and opening of the A-V valves;[16] S_2 occurs at the end of ventricular systole, near the end of the T wave on the ECG (Fig. 5–6) and corresponds to closure of the semilunar (aortic and pulmonic) valves. In dogs and cats, aortic valve closure (A_2) precedes pulmonic valve closure (P_2) by a very short interval, which is usually not detectable by ear, causing S_2 to be heard as a single sound.[12, 14] In dogs, the increase in heart rate accompanying a normal sinus arrhythmia also tends to

nullify the increase in diastolic filling that occurs during inspiration.[18]

SPLIT S_2. Audible splitting during inspiration is occasionally detected in healthy, large-breed dogs. The pulmonic component occurs slightly later in the cardiac cycle than the aortic component. It is best recognized by listening over the pulmonic valve area. Inspiration increases negative intrathoracic pressures, drawing an increased amount of blood into the right ventricle; this requires a longer period for right ventricular ejection, which momentarily delays closure of the pulmonic valve. During expiration, the two components of S_2 approximate each other, and there is no splitting.[12, 16]

Pathologic splitting of S_2 is caused by asynchronous closure of the aortic or pulmonic valve, either from hemodynamic abnormalities or electrical disturbances such as bundle branch block, extrasystoles, or ventricular pacing.[15–19] The most common cause is delayed closure of the pulmonic valve due to pulmonary hypertension (Fig. 5–8) in dogs with heartworm disease and certain congenital heart defects. Here, the interval between A_2 and P_2 varies with respiration, as described earlier. In dogs with an atrial septal defect, this interval does not vary with respiration, and splitting of S_2 is described as "fixed." Delayed closure of the aortic valve results in "paradoxic splitting" of S_2, which is accentuated during expiration. Aortic stenosis, left bundle branch block, and certain ectopic ventricular beats may delay A_2 in dogs. Other potential causes of a split S_2 are listed in Table 5–2.

TABLE 5–2
Mechanisms That May Produce Abnormal Splitting of the Second Heart Sound

A. Pulmonic valve closure follows aortic valve closure (P_2 follows A_2)
   1. Delayed P_2
      - Left-to-right intracardiac shunt (atrial septal defect)*
      - Pulmonary hypertension (heartworm disease)*
      - Pulmonic stenosis*
      - Right bundle branch block*
      - Certain ventricular ectopic beats*
      - Dilatation of the pulmonary artery
   2. Premature A_2
      - Mitral insufficiency
      - Mitral stenosis
      - Left atrial tumors

B. Aortic valve closure follows pulmonic valve closure (paradoxic splitting)
   1. Delayed A_2
      - Aortic stenosis*
      - Left bundle branch block*
      - Certain ectopic ventricular beats*
      - Systemic hypertension

*Mechanisms that have been recognized in the dog.
Modified from Detweiler DK, Patterson DF. Abnormal heart sounds and murmurs of the dog. J Small Anim Pract 8:193, 1967.

EARLY DIASTOLIC SOUNDS

Opening snaps, rarely detected in domestic animals, occur shortly after S_2, at the time of maximal opening of the A-V valves in early diastole. They are a prominent finding in humans with rheumatic mitral valve stenosis but are rarely heard in animals. Mobile atrial tumors can cause similar sounds, which are usually referred to as tumor *plops.* Pericardial *knocks* are early diastolic sounds of similar quality best described in humans with constrictive pericarditis.

THE THIRD HEART SOUND (S_3)

The third heart sound is of low frequency and is generated by rapid ventricular filling. It is not auscultatable in most healthy dogs and cats, but it can sometimes be identified on phonocardiographic recordings as a low-pitched sound occurring 10 to 15 msec after the second heart sound in the dog (Figs. 5–6, 5–9).[12, 14] The intensity is determined by the rapidity of early diastolic filling, the pressure in the atrium, and the distensibility of the ventricle during early diastole.[13, 15, 16] The more compliant the ventricle, the less intense the sound. Auscultatable, loud, third heart sounds are abnormal in the dog and cat and often imply heart failure, especially systolic (myocardial) dysfunction.

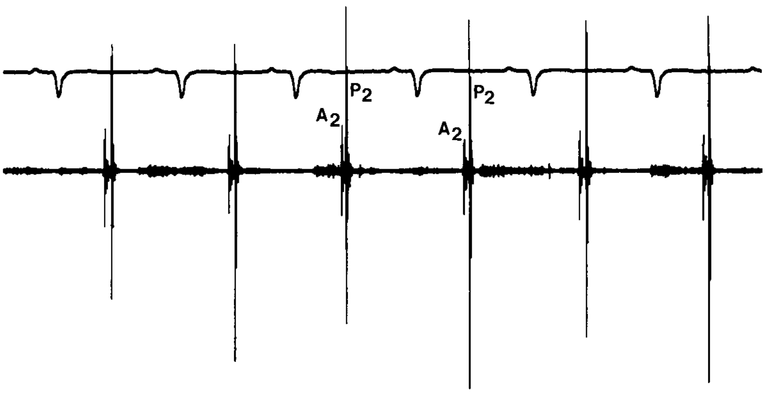


FIGURE 5–8

Phonocardiogram recorded from the pulmonic area of a dog with pulmonary hypertension and a right to left–shunting patent ductus arteriosus. The second heart sound is distinctly split, as is evidenced by its audible components, A_2 (aortic valve closure) and P_2 (pulmonic valve closure). Log scale recording. A simultaneous ECG is displayed above.

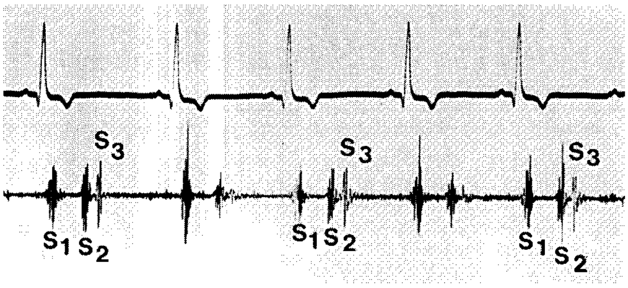


FIGURE 5–9

Phonocardiogram recorded from a Doberman pinscher with dilated cardiomyopathy. Notice the third (S_3) heart sound (protodiastolic gallop), which immediately follows the second (S_2) heart sound. In dogs, auscultation of an S_3 sound strongly suggests the presence of myocardial failure. S_1, first heart sound.

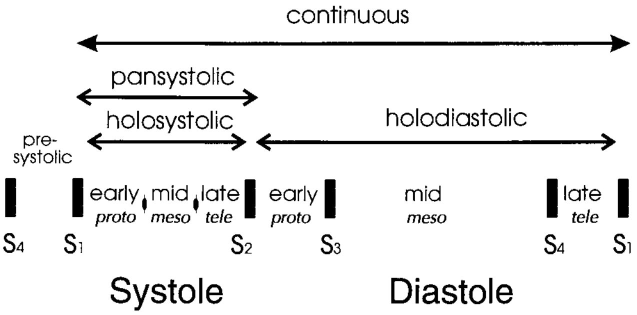


FIGURE 5–10

The timing and duration of systolic and diastolic heart murmurs. The terms "pansystolic" and "holosystolic" are commonly used interchangeably. S_1, first heart sound; S_2, second heart sound; S_3, third heart sound; S_4, fourth heart sound. (Modified from Detweiler DK, Patterson DF. Abnormal heart sounds and murmurs of the dog. J Small Anim Pract 8:193, 1967.)

Other causes of an audible S_3 include mitral regurgitation, hyperthyroidism, and anemia. When S_3 is audible, the heart sounds may be verbally characterized as *lub-dub-thud*. Such sounds are usually best heard with the stethoscope bell positioned near the cardiac apex, along the left sternal border in the left ventricular area.

THE FOURTH HEART SOUND (S_4)

The fourth heart sound is produced by atrial systole. It is always inaudible in normal cats and dogs but may occasionally be demonstrated on a phonocardiogram.[14] Vibrations initiated by forceful ejection of the atrial blood column into an already distended or noncompliant ventricle produce this low-pitched, low-frequency heart sound (Fig. 5–6). When S_4 is audible, the heart sounds may be verbally characterized as *bub-lub-dub*; S_4 is most easily detected using the stethoscope bell positioned near the left cardiac apex.

GALLOP RHYTHMS

A gallop rhythm is a sequence of three sounds consisting of the first and second heart sounds and an extra sound, which is an intensified third or fourth heart sound, or both (Figs. 5–6; 5–9, 5–10, 5–11). Gallop rhythms are classified as protodiastolic (S_3), presystolic (S_4), or as summation gallops (fusion of S_3 and S_4). Gallop heart sounds may originate from either the left or right ventricle and often indicate advanced myocardial disease or heart failure.[14, 17]

The most common *gallop rhythm* auscultated in dogs is a protodiastolic gallop, caused by an accentuated third heart sound. An audible S_3 is most often heard with diastolic ventricular overloading, as in mitral insufficiency, dilated cardiomyopathy, septal defects, or patent ductus arteriosus. In dogs with mitral insufficiency, an accentuated S_3 may be mistaken for the second heart sound if a loud pansystolic murmur ex-

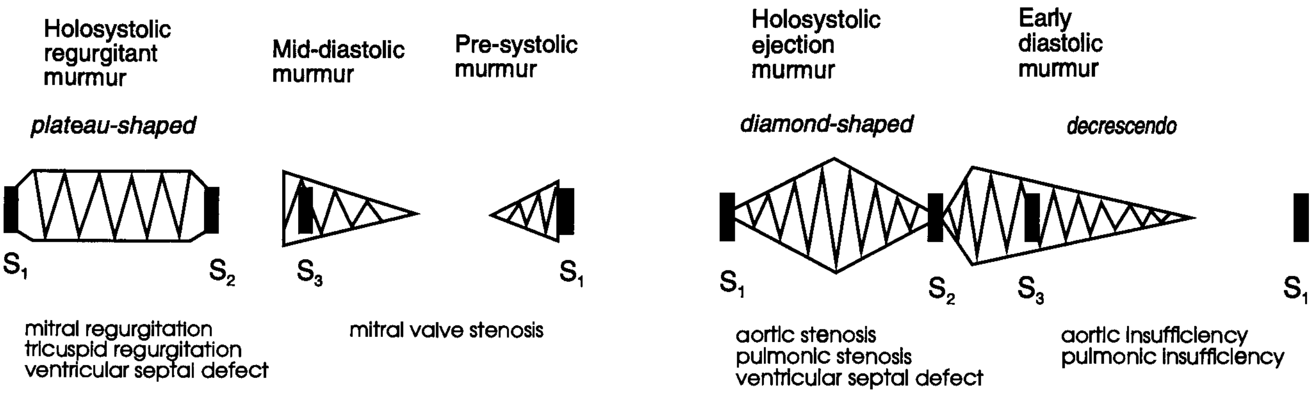


FIGURE 5–11

Contrasting the shape (intensity profile) of a heart murmur, which is often helpful in identifying its origin. The most common murmurs heard in dogs and cats are the plateau-shaped systolic murmur of mitral regurgitation, the diamond-shaped murmur of aortic and pulmonic stenosis, and the continuous murmur of a patent ductus arteriosus. (Modified from Detweiler DK, Patterson DF. Abnormal heart sounds and murmurs of the dog. J Small Anim Pract 8:193, 1967.)

tends through the second heart sound. Protodiastolic gallop sounds in the cat are most commonly associated with congestive (dilated) cardiomyopathy, hyperthyroidism, or severe anemia. A rapid heart rate, particularly in cats, often makes it impossible to determine whether a diastolic filling sound is an S_3, or a summation of the two sounds.

Presystolic gallop sounds heard just before S_1 represent accentuation of S_4. They occur with atrial contraction and follow the P wave on phonocardiographic recordings[12]; S_4 is most likely to be audible in those cardiac conditions associated with marked left ventricular hypertrophy. They are audible only as long as sinus rhythm is preserved and disappear with the onset of atrial fibrillation. In cats, S_4 is commonly associated with diastolic restrictive diseases such as hypertrophic cardiomyopathy (HCM) and left ventricular hypertrophy caused by systemic hypertension or hyperthyroidism. A fourth heart sound is occasionally auscultatable in dogs with profound heart failure due to advanced mitral valvular insufficiency, particularly after rupture of a major chordae tendineae.[14]

When S_4 and S_3 merge, particularly with rapid heart rates, the resulting single accentuated sound is referred to as a *summation gallop*. The summation gallop is caused by the same conditions that produce individual protodiastolic or presystolic sounds.

VARIATIONS IN INTENSITY AND RHYTHM OF HEART SOUNDS

DIMINISHED INTENSITY

Heart sounds are diminished with obesity, emphysema, pleural or pericardial effusions, thoracic masses, diaphragmatic hernias, and when left ventricular contractility and cardiac output are lowered.

INCREASED INTENSITY

Heart sounds are loudest in young, thin animals when the heart rate is rapid. Hyperdynamic states, such as hyperthyroidism, anemia, or fever, may also increase intensity of S_1 and S_2.

VARIATIONS WITH ARRHYTHMIAS

The intensity of S_1 and S_2 may vary with arrhythmias, including sinus arrhythmia of healthy dogs, supraventricular and ventricular premature contractions, atrial fibrillation, ventricular tachycardia, and heart block. These alterations are produced by variations in the location of the atrioventricular valves at the onset of systole and by variable diastolic filling of the ventricles, such that unequal quantities of blood are expelled with successive contractions. The most common cause of heart rate variability in dogs is respiratory sinus arrhythmia. Inspiration causes heart rate to speed up because vagal tone decreases as left atrial filling pressures increase and negative thoracic pressure increases (the Bainbridge reflex). Expiration causes heart rate to slow as vagal tone increases. This waxing and waning of the heart rate, which can be eliminated by pain, excitement, or parasympatholytic drugs, produces a rhythmic variation of the heart sounds.

PREMATURE BEATS AND TACHYARRHYTHMIAS

Single supraventricular and ventricular premature beats are auscultated as early heart sounds of low intensity followed by a pause of variable duration. The pause following atrial and junctional ectopic beats is usually shorter than that following a ventricular premature contraction, but this distinction requires considerable practice to make. It is wiser to identify the nature of an irregular heart rhythm on an ECG. Ventricular ectopic beats may also cause splitting of the first and second heart sounds. The most dramatic examples of heart rate and heart sound variability occur in dogs and cats with atrial fibrillation, an arrhythmia characterized by a rapid, irregular heart rate. The intensity of the first heart sound varies continuously; the second heart sound is absent if the force of contraction is of a magnitude inadequate to open the semilunar valves. If a valvular murmur was present prior to the onset of atrial fibrillation, it may be of variable intensity, especially if the ventricular rate is rapid. The irregularly irregular rhythm of atrial fibrillation has been aptly referred to as *delirium cordis*. Paroxysmal supraventricular or ventricular tachycardias are characterized by bursts of rapid, regular beats that usually cease abruptly.

BRADYARRHYTHMIAS

With first-degree atrioventricular heart block, the first heart sound may be of diminished intensity because the prolonged P-R interval permits the mitral and tricuspid valve leaflets to return passively to a coapted state before ventricular contraction begins. Intermittent pauses in the rhythm are heard in dogs with second-degree heart block, but similar pauses may be caused by pronounced sinus arrhythmia and sinus arrest. In dogs with heart block, a low-pitched atrial sound is sometimes audible during the pause.[20] With complete heart block, two independent rhythms exist.

In addition to the slow but loud and forceful first and second heart sounds produced by the ventricular escape focus, the careful examiner can usually detect the softer and more rapid, low-pitched atrial (S_4) heart sounds.

CARDIAC MURMURS

Murmurs represent sounds of longer duration than the transient heart sounds already described. Heart murmurs arise from turbulent blood flow (vibrations) created when the normal, quiet, laminar flow is disrupted. This is caused by blood flowing through abnormal communications between the cardiac chambers or through stenotic or insufficient valves, or by alterations in blood viscosity or vessel diameter. The relationship of cardiac murmurs to vessel size, flow velocity, and blood viscosity is described by Reynold's number:

$$\text{Reynold's number} = \frac{\text{Radius} \times \text{velocity} \times \text{density}}{\text{Viscosity}}$$

DESCRIPTIVE CHARACTERISTICS OF MURMURS

A number of features may help characterize cardiac murmurs.[12–17, 19, 21]

TIMING. Murmurs can be divided based upon their timing during the cardiac cycle into *systolic, diastolic,* or *continuous* types. Systolic murmurs begin with or after the first heart sound and end with or before the second heart sound. Diastolic murmurs begin with or after the first component of the second heart sound and end prior to the first heart sound. The duration of the murmur within the cardiac cycle may be further modified by terms such as holo- and pansystolic; proto-(early), meso-(mid), or tele-(late) systolic; proto-, meso-, and holodiastolic; and presystolic (Figs. 5–10, 5–11).[12–17, 19, 21]

LOCATION. The location of a murmur relates to the cardiac valve area where it is heard loudest (point of maximal intensity) (Figs. 5–7, 5–11). It may also be heard in other areas where it radiates. Location helps identify the specific valvular lesion, as described under Cardiac Auscultation.

INTENSITY (LOUDNESS). The intensity of a murmur is best communicated using the six grades described by Freeman and Levine.[12, 16, 21] A grade 1/6 murmur is the faintest murmur that can be detected and is heard only with particular effort. A grade 2/6 murmur is a faint murmur clearly heard after a few seconds' auscultation by an experienced examiner. A grade 3/6 murmur is moderately loud and easily heard. A grade 4/6 murmur is a loud murmur that does not produce a palpable thrill. A grade 5/6 murmur is a very loud murmur that produces a thrill (palpable vibration) but is inaudible when the stethoscope is removed from the chest wall. A grade 6/6 murmur is a very loud murmur that produces a thrill (palpable vibration) still audible after the stethoscope is removed from the chest. Adherence to the same grading system permits different clinicians to communicate clearly and concisely.

SHAPE. Murmurs are often described in terms of their profile during the cardiac cycle (Figs. 5–10, 5–11). This corresponds to their shape on a phonocardiogram. Terms that are commonly used include "plateau or "band-shaped" for those murmurs of nearly equal intensity throughout their duration, "decrescendo" for those murmurs that gradually taper off from an initial peak, and "diamond-shaped" or "crescendo-decrescendo" for those murmurs that build to a peak and then gradually diminish.

PITCH OR FREQUENCY. Murmurs may also described as high-, medium-, or low-pitched or of mixed frequency. High-pitched murmurs are heard best with the stethoscope diaphragm, whereas low-frequency murmurs are heard best with the bell. The quality or timbre of a murmur refers to the arrangement of murmur frequency components (purity of the pitch) producing a subjective impression, described in such terms as harsh, blowing, or musical.

RADIATION. Murmurs radiate in the direction of blood flow responsible for the murmur. The pattern of radiation is important in some lesions. For example, the murmur of congenital subaortic stenosis radiates widely—craniodorsally, apically, and even to the head; thus, it may be heard loudly at the right cardiac base. With pulmonic stenosis, the murmur radiates craniodorsally into the main pulmonary artery and thus may be heard loudly at the left cardiac base.

SYSTOLIC HEART MURMURS

INNOCENT AND PHYSIOLOGIC MURMURS

Nonpathologic murmurs include *innocent* murmurs, most commonly detected in young animals with no evidence of structural heart disease, and *physiologic (functional)* murmurs, usually caused by increased cardiac output or decreased blood viscosity. It is often

difficult to distinguish innocent or physiologic murmurs from those due to organic disease.

Innocent and physiologic (functional) murmurs are usually soft (grade 1/6 to 3/6), early to midsystolic, high-frequency murmurs. They are loudest at the aortic or pulmonic valve regions and do not radiate extensively. Such murmurs are of uncertain origin but may be due to increased blood flow velocity and turbulence in the right or left ventricular outflow tracts. The character of the murmur often changes with body position and heart rate, and these murmurs typically disappear in early adult life.

Physiologic (functional) murmurs are common with anemia, hypertension, fever, pregnancy, and hyperthyroidism. It is often impossible to differentiate an innocent from a functional murmur without additional testing. The most common physiologic murmur is caused by decreased blood viscosity from moderate or severe anemia. When the blood hemoglobin level falls below 6 mg/dl, decreased viscosity and increased blood flow velocity produce turbulence. This tends to occur in dogs with a hematocrit of less than 22 to 25 percent and in cats with a hematocrit of less than 18 to 20 percent. Anemic murmurs are usually best heard over the pulmonic or aortic areas during early to midsystole and are typically low-intensity and high-frequency. The murmur typically disappears when anemia is relieved. Diastolic murmurs have occasionally been associated with anemia.

Systolic murmurs of uncertain origin are often heard in cats with hyperthyroidism and in a variety of other systemic disorders. Many of these cats have identifiable left ventricular hypertrophy of uncertain cause. These murmurs are often soft (grade 2/6 to 3/6) and best heard on either side of the sternum over the 5th or 6th intercostal space. Dynamic right ventricular outflow tract obstruction has recently been identified as a common cause of some murmurs in cats in these circumstances.[22] Such obstructions are usually mild, are easily identified by color-flow Doppler echocardiography, and appear to be of little clinical consequence. Systemic conditions that commonly produce murmurs (e.g., anemia, hyperthyroidism) are identified by laboratory testing.

MITRAL INSUFFICIENCY

Although this murmur is usually loudest over the mitral valve area and left atrium, it commonly radiates dorsally and to the right thorax, confounding reliable identification of tricuspid regurgitation. Intensity ranges from grade 1/6 to grade 5/6 but does not reliably indicate severity. Loud murmurs often resonate from small orifices when the volume of regurgitation is small. With severe disease, murmur intensity often declines as the atrial-ventricular pressure difference narrows. Loud murmurs of mitral insufficiency are holosystolic and plateau shaped, whereas soft murmurs commonly occupy only the early portion of systole (Fig. 5–12). Regurgitant murmurs associated with mitral valve prolapse may not develop until mid to late systole. The murmur of mitral insufficiency is typically of mixed frequency and harsh sounding, but it may be high-pitched or musical (whooping) in quality. The pitch of the murmur often varies from examination

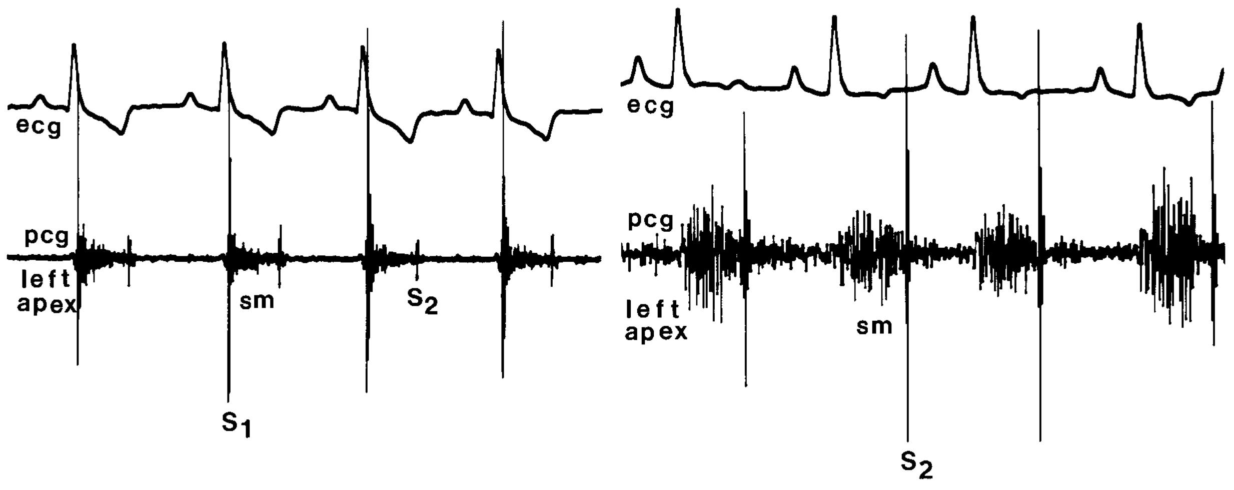


FIGURE 5–12

Phonocardiograms *(pcg)* recorded from two dogs with mitral regurgitation, illustrating the highly variable nature of this murmur. The phonocardiogram on the left, recorded at the left cardiac apex of a dog with mild mitral regurgitation, shows a soft systolic murmur that decreases in intensity in the latter part of systole. The phonocardiogram on the right, recorded at the left cardiac apex of a dog with severe mitral regurgitation and pulmonary hypertension, shows a loud holosystolic murmur and accentuated second heart sound *(S_2)*. *sm,* systolic murmur; *ecg,* electrocardiogram. Log scale recording.

to examination. In dogs with mitral insufficiency, the intensity of the S_1 is often increased. In many affected dogs, S_2 is obscured by the murmur, but in some cases, the pulmonic component of S_2 is accentuated due to coexisting pulmonary hypertension (Fig. 5–12). Dogs with severe mitral regurgitation often manifest protodiastolic or presystolic gallop heart sounds.

Mitral insufficiency results from many diseases. The most common cause in dogs is chronic degenerative valvular disease (myxomatous degeneration).[14] It can also develop when the left ventricle and mitral annulus dilate and the papillary muscles are pulled out of alignment, as in adult dogs with dilated cardiomyopathy and puppies with certain congenital heart defects such as PDA. Congenital malformation of the mitral valve, resulting in valvular insufficiency, is one of the most common congenital heart defects of cats.[23] Mitral regurgitation is common in dogs and cats with HCM and dynamic left ventricular outflow tract obstruction, as the anterior leaflet moves cranially to make contact with the interventricular septum in early to midsystole.[24] The resulting midsystolic regurgitant murmur is difficult to localize on the chest wall as it blends with or is obscured by the systolic ejection murmur. Trivial mitral regurgitation may be detected with color-flow Doppler echo in most cats with cardiomyopathies.

TRICUSPID INSUFFICIENCY

The systolic murmur of tricuspid valve insufficiency is best heard near the right 3rd to 5th intercostal spaces at the costochondral junction. Unfortunately, the murmur of mitral insufficiency radiates to that area as well, and these murmurs may be very difficult or impossible to differentiate. The intensity and duration of murmurs arising from the tricuspid valve tend to vary more with respiration than do mitral murmurs. Isolated tricuspid insufficiency secondary to myxomatous degeneration of the valve occurs, particularly in cocker spaniels and Dachshunds, but this is an uncommon finding. Tricuspid regurgitation also occurs because of congenital malformation of the tricuspid valve. Dilatation of the right ventricle, as occurs with pulmonary hypertension and cardiomyopathy, can also cause tricuspid valve insufficiency.

AORTIC STENOSIS

In dogs, acquired or congenital aortic valve stenosis is rare; however, subvalvular aortic stenosis (SAS) is one of the most common canine congenital heart defects. All these disorders are uncommon in cats. The murmur of valvular and subvalvular aortic stenosis is a systolic crescendo-decrescendo, or diamond-shaped murmur, heard best at the left heart base or right cranial thorax (Fig. 5–13).[15] Mild obstructions cause soft murmurs that are difficult to distinguish from innocent or functional murmurs.[24] The intensity of such murmurs increases substantially following exercise, as a larger stroke volume is ejected into the aortic root. Unfortunately, innocent and functional murmurs often behave similarly. With moderate-to-severe SAS, the murmur grows louder and longer in duration; is usually harsh and of mixed frequency; and often radiates into the thoracic inlet and up the neck along the carotid arteries. If the murmur is sufficiently intense, it is accompanied by a precordial thrill. Aortic ejection sounds may occur with subvalvular aortic stenosis and may be related to poststenotic dilatation of the aorta, or opening of a thickened aortic valve. Color-flow Doppler echo studies indicate that SAS is usually associated with mild aortic insufficiency. In most cases, the

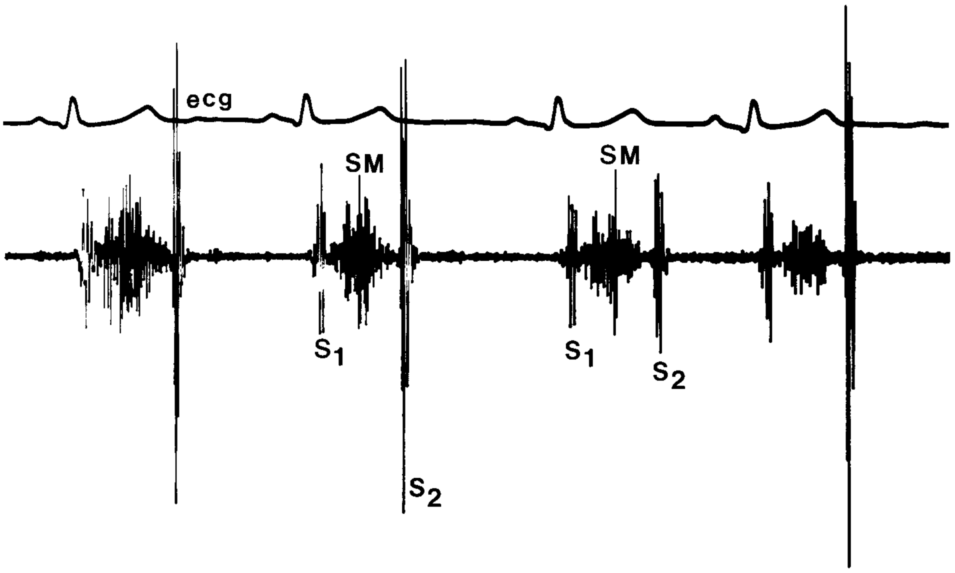


FIGURE 5–13

Phonocardiogram recorded from a dog with congenital subaortic stenosis. The systolic ejection murmur of aortic stenosis is diamond-shaped, best heard and recorded with the stethoscope (or stethophone) placed over the aortic valve area. *ecg*, electrocardiogram; *SM*, systolic murmur; *S_1*, first heart sound; *S_2*, second heart sound. Log scale recording.

diastolic leak is minor and there is no audible evidence of a diastolic murmur.

Dynamic left ventricular outflow tract obstruction occurs in dogs and cats with HCM as well as in certain congenital heart defects causing interventricular septal hypertrophy.[24] Such murmurs may be absent at rest but very loud during and following exercise. The mechanism is demonstrated by echocardiography, using provocative maneuvers that increase myocardial contractility, decrease end-diastolic left ventricular volume, or reduce afterload. Murmur onset and duration are coincident with systolic anterior motion of the mitral valve. Dynamic obstruction is the most common cause of ejection murmurs in cats with HCM.

PULMONIC STENOSIS

A high-frequency systolic ejection murmur, best heard at the left-sided heart base over the pulmonic valve, is characteristic. Murmur intensity and duration vary with the severity of the stenosis. As the pressure gradient between the right ventricle and pulmonary artery widens, the murmur becomes louder and peaks later in systole.[14, 16] The murmur of pulmonic stenosis is typically a crescendo-decrescendo (diamond-shaped), holosystolic murmur with maximum intensity in midsystole. Loud murmurs may be accompanied by a precordial thrill palpable over the pulmonic area on the left cranial thorax. The murmur of pulmonic stenosis tends not to radiate as widely as the murmur of subaortic stenosis. Splitting of S_2 may be noted on phonocardiographic recordings, but this is usually not heard because of the loud murmur.

VENTRICULAR SEPTAL DEFECT

The murmur caused by a restrictive ventricular septal defect (VSD) is loud, harsh, and typically best heard on the right cranial thorax. The shape and quality of these murmurs vary tremendously, but they are often mid- to high-frequency holosystolic murmurs, frequently accompanied by a thrill at the point of maximal intensity.[25] Murmur intensity and duration may be reduced if the VSD is large and pulmonary hypertension develops. With severe pulmonary hypertension, the murmur is absent and the second heart sound is split.[16]

ATRIAL SEPTAL DEFECT

Auscultatory findings with atrial septal defect (ASD) include a systolic ejection murmur loudest over the pulmonic area occurring in combination with fixed splitting of the second heart sound.[26] The systolic murmur is caused by increased blood flow across a normal pulmonic valve. Delayed closure of the pulmonic valve results from a combination of hemodynamic and electrical factors. Relative to the left side of the heart, the right ventricle must expel an increased volume of blood. In addition, conduction disturbances leading to delayed right ventricular activation are common in dogs with an ASD.

DIASTOLIC HEART MURMURS

MITRAL STENOSIS

Mitral stenosis (MS) is uncommon in dogs and cats, and auscultatory features are not well characterized.[27, 28] In dogs, MS is usually a congenital abnormality. Most reported cases were detected in dogs with concurrent subaortic stenosis. A diastolic murmur was heard in the left apical area in 4 of the 15 reported dogs.[28] In the same report, a left apical holosystolic murmur compatible with mitral insufficiency was heard in eight dogs. The murmur of MS is low-pitched, and it begins in mid-diastole. In human patients, the duration of the murmur correlates with the severity of the obstruction.[13, 14] Presystolic accentuation of the murmur results when transvalvular blood flow is increased following contraction of the atrium. In the small number of affected animals we examined, diastolic murmurs were usually present, but they were often subtle and easily could be overlooked (Fig. 5–14).

AORTIC INSUFFICIENCY

In adult dogs, aortic insufficiency results most often from bacterial endocarditis.[29] It also occurs as an isolated congenital heart defect, in association with subaortic stenosis, or as an unwanted complication of a ventricular septal defect.[30] Insufficiency of the aortic valve results in a soft, blowing, decrescendo heart murmur beginning immediately after the second heart sound. It is frequently accompanied by a midsystolic, ejection type of murmur. Such murmurs are usually best heard over the aortic area or at the cardiac apex. In dogs with severe aortic regurgitation, a presystolic murmur, referred to as an Austin Flint murmur, may also be heard as the mitral valve closes prematurely, causing disturbed diastolic flow through the mitral orifice. The presence of both systolic and diastolic heart murmurs, which in combination have a distinct "to-and-fro" quality, must not be confused with the truly continuous murmur of an arteriovenous fistula or patent ductus arteriosus.

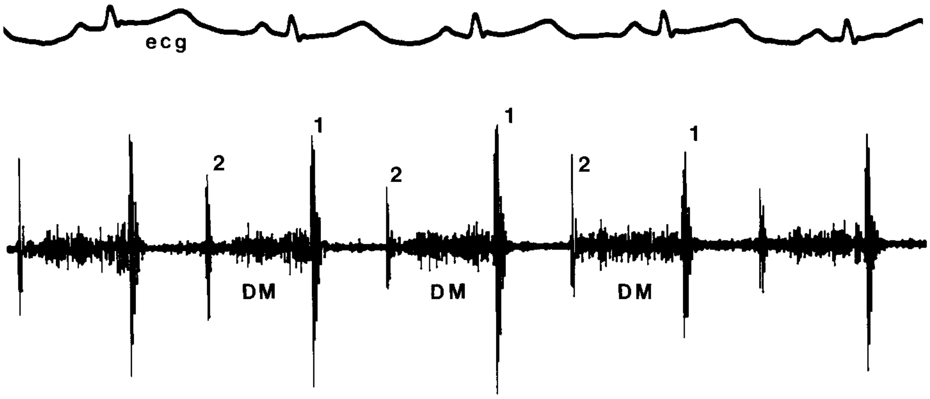


FIGURE 5-14

Phonocardiogram recorded from a cat with mitral valve stenosis. Notice the presystolic accentuation of this mid-diastolic murmur. Diastolic murmurs *(DM)* are uncommon in dogs and cats. Compare the timing of this diastolic murmur to the systolic murmurs in Figures 5-14 and 5-15. *ecg,* electrocardiogram; *1,* first heart sound; *2,* second heart sound. Log scale recording.

PULMONIC INSUFFICIENCY

Isolated pulmonic insufficiency of sufficient magnitude to produce an audible murmur is uncommon. Few dogs with isolated congenital pulmonic insufficiency have been described.[23] The diastolic murmur of isolated pulmonic insufficiency begins in early diastole. It is soft, is decrescendo in shape, and is usually accompanied by an ejection murmur also located over the pulmonic valve area. The murmur of pulmonic insufficiency is sometimes detected in dogs with pulmonic stenosis or a patent ductus arteriosus. When pulmonic insufficiency develops as a consequence of pulmonary hypertension, the murmur is usually, louder, harsher, and longer in duration.[31]

CONTINUOUS MURMURS

The characteristic murmur of a PDA is a continuous systolic and diastolic "machinery-like" murmur that is best heard over the aortic and pulmonic valve regions.[12, 14] The continuous murmur of a PDA waxes and wanes during the cardiac cycle and reaches peak intensity near the time of the second heart sound (Fig. 5-15).[12, 16] It is best heard at the left heart base but radiates widely in some animals. The distinctive continuous murmur occurs as blood flows from the high-pressure aorta to the low-pressure pulmonary artery, producing turbulence. Pulmonic and mitral valve insufficiency are observed in many dogs with a PDA, contributing to the acoustic events.

Although detection of a continuous murmur is highly suggestive of a PDA, it is not a pathognomonic finding. Pulmonary arteriovenous fistulas produce continuous murmurs, as do coronary arteriovenous fistulas. A continuous murmur also results when a coronary artery or ruptured coronary sinus aneurysm communicates directly with the right atrium. All these defects are quite rare. The murmur of a PDA is not always continuous. The development of pulmonary hypertension can cause attenuation and eventual disappearance of the diastolic murmur.[16]

THE ARTERIAL PULSE AND THE EXTREMITIES

Examination of the extremities is performed to (1) detect regional or generalized perfusion deficits, (2)

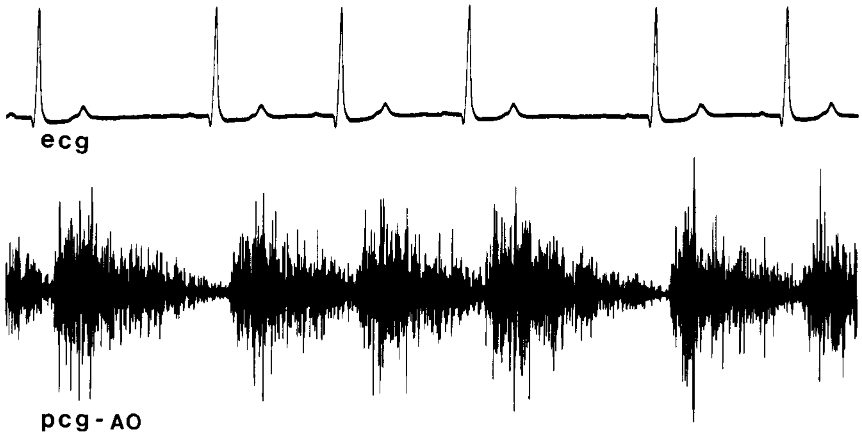


FIGURE 5-15

Phonocardiogram *(pcg)* recorded from a dog with patent ductus arteriosus. This distinctive continuous murmur is best heard at the left heart base. The peak murmur intensity occurs just after the T wave of the electrocardiogram *(ecg),* near the time when the second heart sound would be heard. Log scale recording.

evaluate the patency of the peripheral veins, and (3) assess the integrity of regional lymphatics. The apparent pulse size and character are determined by the stroke volume, rate of ejection, distensibility of the vascular bed, the peripheral resistance, the systolic and diastolic pressures, and many other factors (Fig. 5–16). A small, weak pulse is often found in conditions with a small stroke volume, increased peripheral resistance, and narrow pulse pressure. One common cause of this type of pulse is left ventricular failure.[32] Small or weak pulses with a delayed systolic peak *(parvus et tardus)* are often noted in dogs with moderate-to-severe SAS. When the pulse is large and strong and the contour is otherwise normal, it is called a bounding, or "waterhammer," pulse. Such pulses are commonly encountered in animals with a PDA, peripheral A-V fistula, or aortic insufficiency (Corrigan's pulse). Patients with mitral insufficiency or VSD often have abrupt, brisk, or jerky pulses because a greater than normal percentage of the stroke volume is ejected in early systole. Various specific arterial pulse abnormalities have been described in humans. The normal arterial pulse contour consists of three parts—the ascending limb, peak, and descending limb. Anacrotic and dicrotic pulses do not occur or are not appreciated in dogs or cats. Other abnormalities such as pulsus alternans, pulsus bigeminus, and pulsus paradoxus can be easily identified in dogs.

Pulsus alternans is identified when the arterial pulse alternates between strong and weak pulses while the patient is in sinus rhythm.[33] In extreme cases, the alternating weak pulses become imperceptible. Pulsus alternans is a sign of profound myocardial depression. In accordance, we have detected this pulse pattern most often in dogs with dilated cardiomyopathy.

Pulsus bigeminus is caused when pulse strength alternates with certain arrhythmias, most commonly ventricular bigeminy. It is easily identified since the weak pulse typically follows a shorter interval than the stronger pulse.

Pulsus paradoxus is an inspiratory fall in systemic arterial pressure exceeding 10 mmHg. This is at or just below the level detectable by physical palpation of a peripheral artery. It is detected most commonly in dogs with pericardial effusion and cardiac tamponade. In this circumstance, weak pulses may disappear entirely for several beats during inspiration (chapter 29).

Partial or complete obstruction of the peripheral arteries is usually due to systemic thromboembolism. In dogs, primary causes include bacterial endocarditis, hyperadrenocorticism, and certain protein-losing glomerulopathies (amyloidosis). The most common cause of systemic thromboembolism in cats is myocardial disease. Physical abnormalities resulting from vascular obstruction include inability to palpate an arterial pulse, coolness of the affected extremities, muscular rigidity

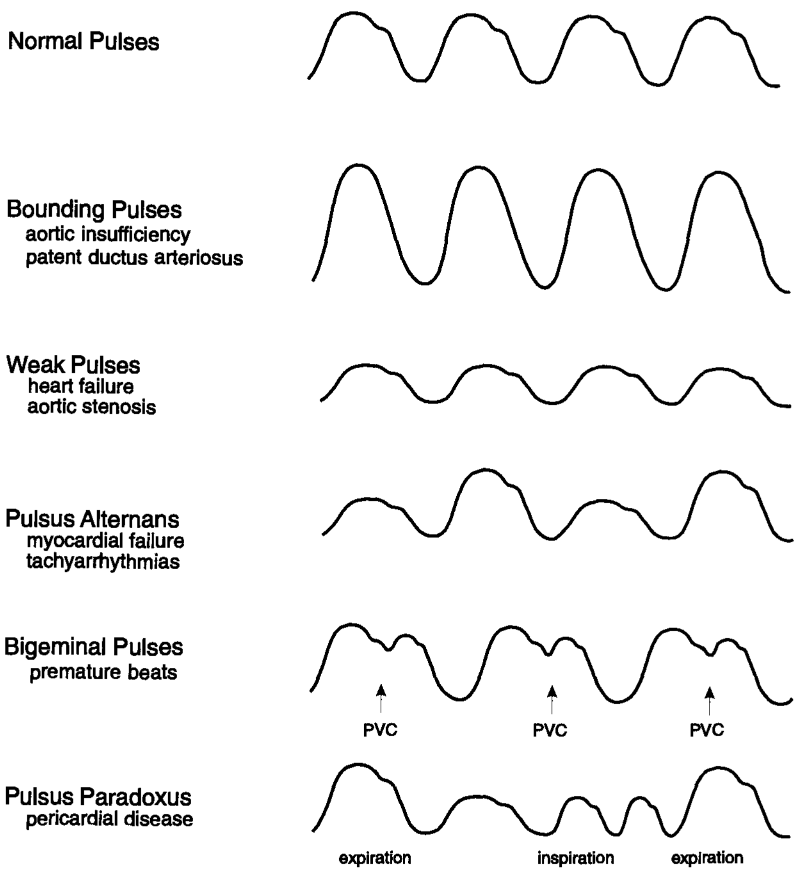


FIGURE 5–16

Arterial pulse variations. Palpable abnormalities of the arterial pulses are common in dogs and cats with heart disease. The top tracing shows the contour of the normal femoral artery pulse; tracings below show how the arterial pulse changes with a variety of cardiovascular disorders. *PVC,* premature ventricular complex.

and pain, and pallor or cyanosis of the footpads and nailbeds. Obliterative changes in the femoral arteries of Cavalier King Charles spaniels with mitral regurgitation have been described,[34] although the etiology is unexplained.

REFERENCES

1. Detweiler DK, Patterson DF, Luginbühil H. Diseases of the cardiovascular system. *In* Catcott EJ (ed): Canine Medicine: A Text and Reference Work, Santa Barabara, California, American Veterinary Publishers, Inc., 1968, p 589
2. Freeman LM. The role of cytokines in cardiac cachexia. Proc 14th Ann Vet Med Forum, 1996, p 240
3. Jacobs, G. Cyanosis. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 192
4. Littman MP. Spontaneous systemic hypertension in 24 cats. J Vet Intern Med 8:79, 1994
5. Sisson DD, Knight DH, Helinski C, et al. Plasma taurine concentrations and M-mode echocardiographic measures in healthy cats and cats with dilated cardiomyopathy. J Vet Intern Med 5:232, 1991
6. Constant J. Bedside Cardiology. 3rd ed. Boston, Little, Brown & Co., 1985, p 95
7. Ewy GA. The abdominojugular test: Technique and hemodynamic correlates. Ann Intern Med 109:456, 1988
8. Selig MB. Stethoscopic and phonoaudio devices: Historical and future perspectives. Am Heart J 126:262, 1993
9. Butterworth JS, Chassin MR, McGrath R, et al. Cardiac Auscultation. New York, Grune and Stratton, 1960
10. Johnston FD. Symposium of cardiovascular sound. II. Clinical aspects. Circulation 16:421, 1957
11. Groom D. The effect of background noise on cardiac auscultation. Am Heart J 52:781, 1956
12. Detweiler DK, Patterson DF. A phonograph record of heart sounds and murmurs of the dog. Ann NY Acad Sci 127:322, 1965
13. Ravin A. Auscultation of the Heart. 2nd ed. Chicago, Year Book Medical Publishers, 1967
14. Ettinger SJ, Suter PF. Canine Cardiology. Philadelphia, WB Saunders, 1970, p 12
15. Tilkian AG, Conover MB. Understanding Heart Sounds and Murmurs. 2nd ed. Philadelphia, WB Saunders, 1984
16. Perloff JK. Heart sounds and murmurs: Physiological mechanisms. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB Saunders, 1992, p 43
17. Gompf RE. The clinical approach to heart disease: History and physical examination. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 29
18. Patterson DF, Detweiler DK. The diagnostic significance of splitting of the second heart sound in the dog. Zentralbl Veterinarmed 10:121, 1963
19. Detweiler DK, Patterson DF. Abnormal heart sounds and murmurs of the dog. J Small Anim Pract 8:193, 1967
20. Ettinger SJ. Isoproterenol treatment of atrioventricular block in the dog. J Am Vet Med Assoc 154:398, 1969
21. Ware W. Abnormal heart sounds and heart murmurs. *In* Ettinger SJ, Feldman EC (eds): A Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 86
22. Rishniw M, Thomas WP, Kienle RD. Dynamic right midventricular obstruction in 50 cats; Abstract. J Vet Intern Med 10:159, 1996
23. Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds): A Textbook of Veterinary Internal Medicine. 4th ed, Philadelphia, WB Saunders, 1995, p 892
24. Sisson D, Thomas WP. Myocardial diseases of the dog and cat. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 995
25. Hamlin RL, Smetzer DL, Smith, CR. Interventricular septal defect (Roger's disease) in the dog. J Am Vet Med Assoc 145:131, 1964
26. Hamlin RL, Smith CR, Smetzer DL. Ostium secundum type interatrial septal defects in the dog. J Am Vet Med Assoc 143:149, 1963
27. Tashjian RJ, McCoy JR. Acquired mitral stenosis resulting in left atrial dilatation with thrombosis. Cornell Vet 50:485, 1960
28. Lehmkuhl LB, Ware WA, Bonagura JD. Mitral stenosis in 15 dogs. J Vet Intern Med 8:2, 1994
29. Sisson D, Thomas WP. Infective endocarditis of the aortic valve in the dog. J Am Vet Med Assoc 184:570, 1984
30. Sisson D, Luethy M, Thomas WP. Ventricular septal defect accompanied by aortic regurgitation in 5 dogs. J Am Anim Hosp Assoc 27:441, 1991
31. Hahn AJ. Auscultation of the canine heart. Part IV. Murmurs. Small Anim Clinician 2:13, 1962
32. Goodwin JK. Pulse alterations. *In* Ettinger SJ, Feldman EC (eds): A Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 89
33. D'Cruz I, Cohen HC, Prabhu R, et al. Echocardiography in mechanical alternans. Circulation 54:97, 1976
34. Buchanan JW. Cardiovascular pathology in Cavalier King Charles spaniels. Proc 13th Am Coll Vet Intern Med Forum, 1995, p 292

III

Diagnostic Methods

6

Electrocardiography

MICHAEL S. MILLER

LARRY P. TILLEY

FRANCIS W. K. SMITH, JR.

PHILIP R. FOX

PRINCIPLES OF ELECTROCARDIOGRAPHY

The electrocardiogram (ECG) is a record of the average electrical potential generated in the heart muscle graphed in voltage and time during the cardiac cycle. Intracellular and extracellular ionic gradients move across semipermeable membranes and result in cellular transmembrane action potentials. The summation or subtraction of these electric charges generated during the cardiac cycle results in a vector that acts as a dipole. It is measured by the ECG at the body surface.[1] Extracardiac factors may influence the ECG, including body tissues with different conductive properties and body structure.

Normally, each ECG segment is sequentially generated from a specific cardiac region. The P wave, QRS complex, and T wave are the recognizable deflections of the ECG trace and indicate atrial depolarization (P), ventricular depolarization (QRS), and ventricular repolarization (T) (Fig. 6–1).

HISTORICAL PERSPECTIVES

In 1856, Kolliker and Müller[2, 3] demonstrated that the beating heart generates electric current. In the experiment, a frog muscle rhythmically twitched when in contact with a contracting ventricle. In 1887, Waller[4] used a capillary electrometer to measure current associated with cardiac electrical activity from the body surface. However, accurate quantitative measurements of cardiac electric activity awaited Einthoven's string galvanometer in 1902.[5] Einthoven also developed the bipolar triaxial lead system and named the specific waveforms produced on the electrocardiogram "P-QRS-T complexes." Although his 600-lb instrument was used for research, its clinical application developed rapidly. Sir Thomas Lewis used Einthoven's technology and expanded it in clinical cardiology. Lewis[6] wrote the first authoritative book on clinical electrocardiography in 1913. Wilson and colleagues developed the concept of a central terminal in 1933,[7] which led to the development of unipolar electrocardiography.[8] The central terminal provides an indifferent electrode with small potential change throughout the cardiac cycle.

Although Waller and Einthoven had recorded canine ECGs, Norr[9] was the first to approach electrocardiography in the dog clinically. Veterinarians expanded clinical and research applications for electrocardiography in the 1950s through 1990s.[10–21]

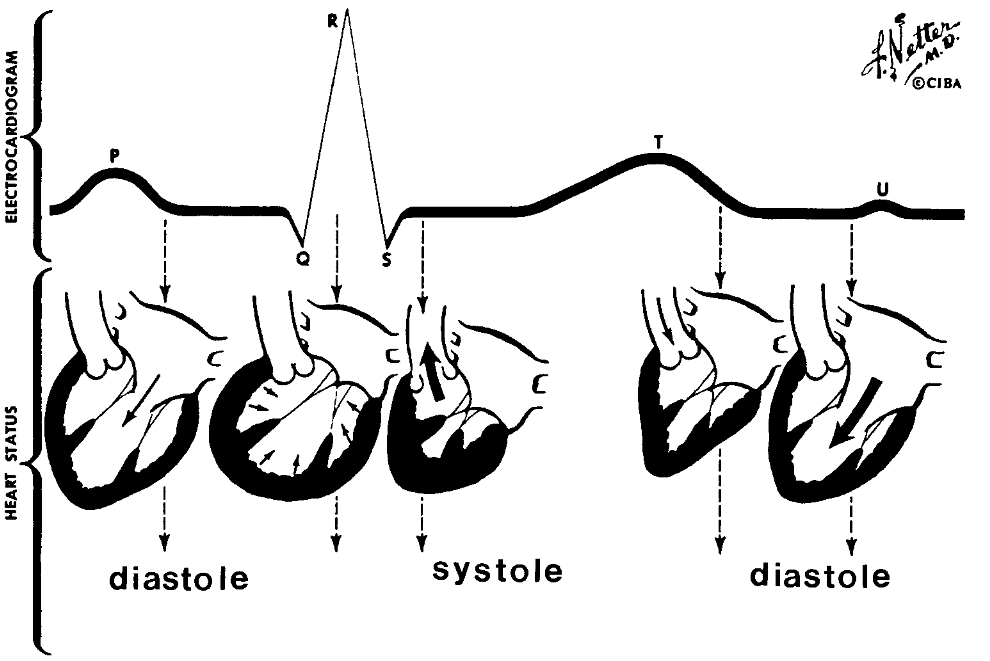


FIGURE 6–1

Electrocardiographic waveforms indicating depolarization and repolarization correlated with mechanical events of the cardiac cycle. (Copyright 1968. Novartis. Reprinted with permission from Clinical Symposia, Vol. 10/1, illustrated by Frank Netter, MD. All rights reserved.)

RECORDING THE ELECTROCARDIOGRAM

The ECG is a moving record of the deflections generated by the electrocardiograph stylus calibrated in voltage (vertical axis) and time (horizontal axis). Electrocardiographic electrodes (leads) sample cardiac potentials at the body surface. These are measured by the electrocardiograph (galvanometer) and recorded on standardized graph paper inscribed with 1-mm spaced horizontal and vertical lines[21–25] (Fig. 6–2). The electrocardiograph can combine the electrodes on the body (right and left arms, left leg, and exploring electrode) into the specific combinations or leads (Table 6–1). They include bipolar standard limb leads I, II, and III (Fig. 6–3), unipolar limb leads aV_R, aV_L, and aV_F (Fig. 6–4), and unipolar precordial (thoracic) leads CV_6LL (V_2), CV_6LU (V_4), CV_5RL (rV_2), and V_{10}.

Right lateral recumbency is the standard body position for ECG recording in the eupneic animal (Fig. 6–5). Electrodes should be placed just above the olecranon and over the patellar ligaments for bipolar standard and augmented unipolar limb leads. Alcohol or conducting paste is applied to the skin and electrodes. If tachypnea or dyspnea is evident, the ECG should be

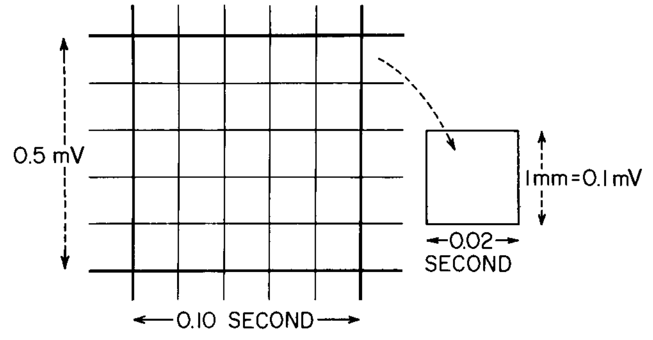


FIGURE 6–2

Electrocardiographic grid lines. At the standard paper speed of 50 mm/sec, the interval between two heavily drawn vertical lines is 0.10 second and between two fine vertical lines, 0.02 second. At normal standardization, 10 mm (10 small boxes) = 1.0 mV, so each small vertical box = 0.1 mV. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

TABLE 6–1
Electrocardiograph Lead Systems

Bipolar standard limb leads
Lead I: right arm (−) compared with left arm (+)
Lead II: right arm (−) compared with left leg (+)
Lead III: left arm (−) compared with left leg (+)
Augmented unipolar limb leads
Lead aV_R: right arm (+) compared with left arm and left leg (−)
Lead aV_L: left arm (+) compared with right arm and left leg (−)
Lead aV_F: left leg (+) compared with right and left arms (−)
Special leads
Unipolar precordial chest leads
Lead CV_5RL (rV_2): fifth right intercostal space near edge of sternum
Lead CV_6LL (V_2): sixth left intercostal space near edge of sternum
Lead CV_6LU (V_4): sixth left intercostal space at costochondral junction
Lead V_{10}: over dorsal spinous process of seventh thoracic vertebra
Modified orthogonal lead systems
Lead X: lead I; right (−) to left (+)
Lead Y: lead aV_F, cranial (−) to caudal (+)
Lead Z: lead V_{10}; ventral (−) to dorsal (+)

From Tilley LP. Essentials of Canine and Feline Electrocardiography. Interpretation and Management. 3rd ed. Philadelphia, Lea & Febiger, 1992.

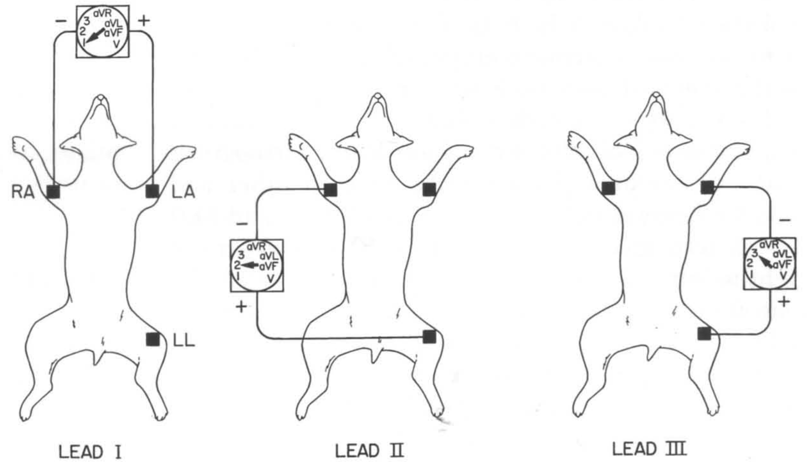


FIGURE 6–3

Bipolar standard leads I, II, and III. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

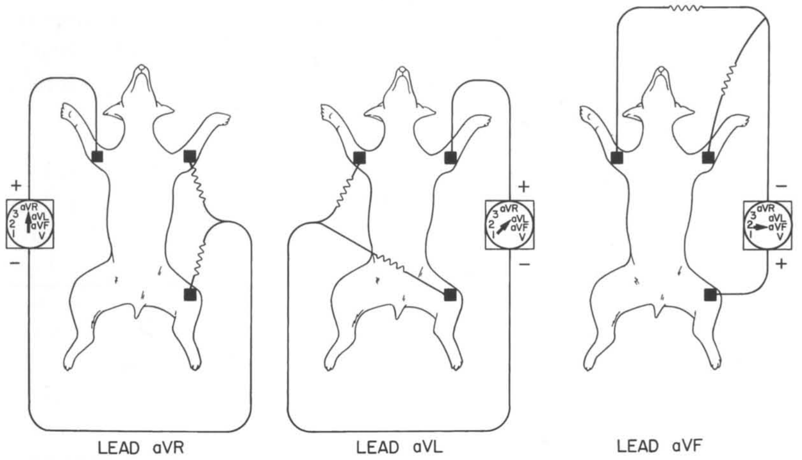


FIGURE 6–4

Augmented unipolar limb leads aVR, aVL, and aVF. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

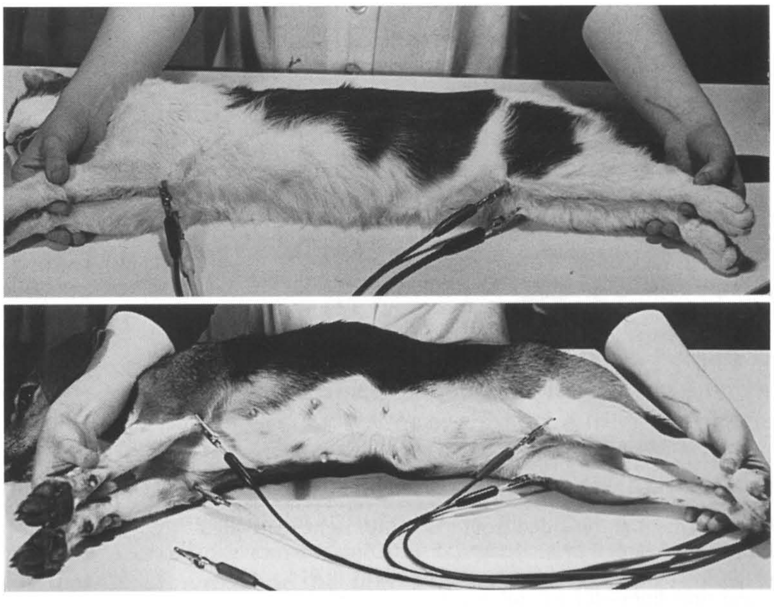


FIGURE 6–5

Right lateral recumbency position for recording the ECG in the eupneic animal. Proper electrode placement is illustrated. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

recorded with the animal standing or in a sternal position to reduce the stress of examination. Precordial chest leads may be helpful in confirming cardiac chamber enlargement; in emphasizing the deflections of the standard limb leads (e.g., it may be important if P waves are not clearly visible); and for confirming data recorded on the other limb leads. Orthogonal leads are oriented perpendicular to each other and view the heart in different planes (leads X, Y, and Z).[21] The X lead measures the frontal plan directed from right to left and is approximated by lead I. The Y lead axis indicates a midsagittal plane oriented craniocaudally and is approximated by lead aV_F. The Z lead represents the transverse plane directed ventral to dorsal and is approximated by lead V_{10}. The orthogonal leads can be used to generate a *vectorcardiogram* (Fig. 6–6). Orthogonal lead systems (McFee, Schmidt, and Frank lead systems) require utilization of multiple electrodes at precise body locations.

Technical or mechanical problems that are superimposed on and distort the normal P-QRS-T complexes are known as *artifact*. For accurate ECG interpretation, it is essential to recognize artifact and eliminate the source. Electric 60-cycle "noise" may be due to poor electric grounding (of the electrocardiograph, the animal, or table on which the animal is positioned), or adjacent lights, or electrical equipment. It is recognized on the ECG tracing as a regular sequence of fine, sharp, vertical oscillations. The placement of a hand on the animal's thorax or blowing into the animal's face may aid in minimizing muscular tremor and respiratory motion. Artifact may also be reduced by positioning the electrode clips correctly, using appropriate conductive gel, and preventing the electrodes or wires from moving during respiration.

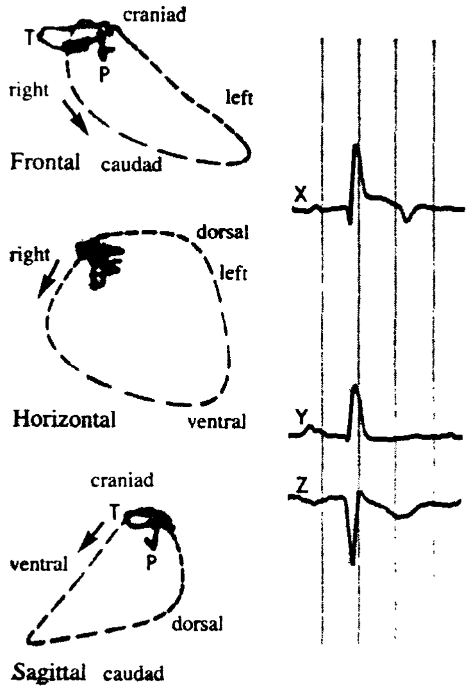


FIGURE 6–6

Vectorcardiogram recorded from a dog with right ventricular hypertrophy caused by heartworm disease. Initial ventricular forces are prolonged and oriented toward the right (0.014 second). Scalar time lines—0.1 second; teardrops—0.002 second. (From Ettinger SJ, Suter PF: Canine Cardiology. Philadelphia, WB Saunders, 1970, with permission.)

VECTORCARDIOGRAPHY

The vectorcardiogram is another method of recording electric potentials generated from the cardiac cycle (Fig. 6–6). Using a cathode ray oscilloscope, it may be projected in the frontal, horizontal, and sagittal planes. In contrast to an ECG lead that records instantaneous vectors (i.e., electric potentials) in a single axis, the vectorcardiogram records electric events simultaneously in two perpendicular axes as a loop recording.[3, 19, 24, 26] Vectorcardiography is useful in teaching and research[24a] but is rarely performed in clinical practice.

ELECTROPHYSIOLOGIC PRINCIPLES

TRANSMEMBRANE ACTION POTENTIALS

A myocardial cell transmembrane action potential may be divided into four recognizable phases[1, 22–27] (Fig. 6–7). A negative resting potential, termed phase 4, is characterized by an intracellular-to-extracellular electrochemical gradient of approximately −90 mV. The rapid action potential upstroke, or phase 0, represents cellular *depolarization* due to rapid movement of extracellular-to-intracellular sodium ions through fast sodium channels. Phase 1 is termed the overshoot and is caused by excessive sodium ion entry into the cells. As sodium influx stops, the membrane potential drops toward 0 mV. The slow calcium ion channels permit extracellular-to-intracellular calcium flow causing the plateau, or phase 2 of the action potential. During the plateau phase, the cardiac cell cannot be stimulated *(refractory period)*. This allows for coordination between cellular electrical and mechanical functions. At the end of the plateau, the slow intracellular calcium channels close, potassium flow out of the cell persists, and intracellular negativity, or phase 3, is re-established (termed "repolarization"). The cell at the resting potential can then be activated by an electrical or chemical stimulus and is said to be *excitable* (chapter 16).

Although transmembrane action potentials of atrial

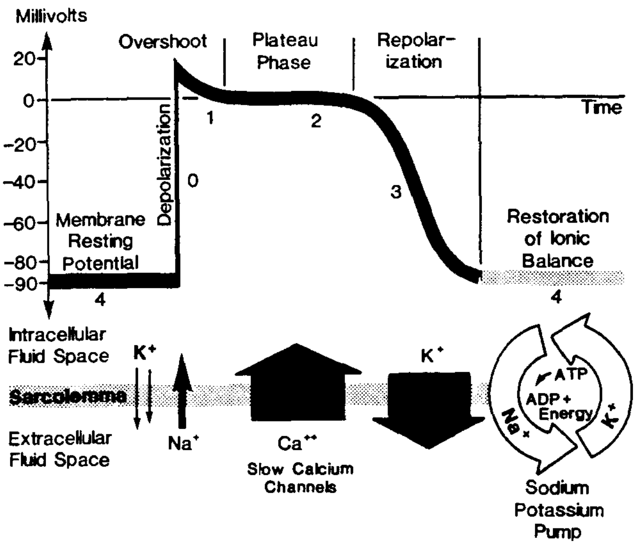


FIGURE 6–7

Phases and ionic gradients of the cardiac cell transmembrane action potential. (From Lipman BS, Dunn M, Massie E: Clinical Electrocardiography. 7th ed. Chicago, Year Book Medical Publishers, 1984, with permission.)

and ventricular fibers are similar, they differ from pacemaker cell transmembrane potentials (see Figs. 16–1, 16–2). Pacemaker cells possess automaticity characterized by a low resting membrane potential; slow activation during phase 0; short action potential duration; no overshoot; and spontaneous depolarization during phase 4 until the threshold potential is reached. Automaticity is the capability of a cell to depolarize spontaneously, reach threshold potential, and initiate an action potential.[1, 23] Pacemaker cells have a slower upstroke and lower amplitude than myocardial cells. *Conductivity* is the ability of a cell's action potential to produce electric current that stimulates adjacent cell membranes to their threshold potential and to depolarize.

Other cardiac tissues, including cells in the atria, mitral and tricuspid valves, distal atrioventricular (AV) nodal and AV junctional tissues, and the His-Purkinje system, are capable of automaticity. Normally, these latent pacemaker cells reach threshold later than do sinus node cells and thus are discharged before they automatically depolarize. Properties of automaticity, excitability, conductivity, and refractoriness are important in arrhythmia genesis and therapy.

THE SURFACE ELECTROCARDIOGRAM

Abnormalities in cellular depolarization result in QRS complex alterations. Disturbances in repolarization are reflected by changes in the ST segment or T wave. These relationships between cellular changes and surface ECG waveforms are described next and may be related to cardiac or extracardiac disorders.

The ECG waveforms are scalar records of cardiac electrical potentials as projected at the body surface.[1, 23, 24] A scalar quantity has magnitude and sense (i.e., positive or negative), but no direction. A vector quantity has magnitude, sense, and direction. It may be the result of two or more scalar forces (e.g., two ECG leads) or multiple vector forces. The surface ECG is a recording of the mathematical summation of electric activity from all individual myocytes. This electric activity is modified by the spatial relationships of each myocyte to each other, the time sequence of activation of the cardiac cells (i.e., they do not all depolarize simultaneously), and the characteristics of the body as an electric field.[22, 25] For example, the first and last ventricular myocardial cells that are stimulated depolarize asynchronously. A difference in electric potential occurs during this depolarization period that results in the QRS complex.

EQUIVALENT DIPOLE THEORY

A review of the dipole hypothesis can provide a theoretic basis for clinical ECG interpretation. A single pair of equal and opposite charges that are in close proximity to each other constitute an electrical generator, termed a dipole. If the dipole is immersed in a conducting medium (e.g., body fluids), the dipole will generate an electric field throughout the conducting medium.[22, 24–27] The electric potential measured at any position in the electric field depends on the position of the recording electrode with respect to the positive and negative charges of the dipole. If any two points (electrodes) with a different potential in the electric field are connected by a superior electric conductor (e.g., the ECG lead wires), the potential difference between the electrodes will result in a flow of current through the wires. This electromotive force, or voltage, is the quantity measured by the surface ECG.

Numerous surface dipoles are formed by the individual myocardial cells and muscle bundles, and they move during the depolarization-repolarization process (Fig. 6–8). They create an electric field in the surrounding body tissues and can be represented by vectors that point toward the positive charge.

Dipoles differ in orientation and polarity because of their varied spatial relationships in the multidimensional heart. At any given instant during ventricular depolarization or repolarization, all the dipoles can be integrated and a resultant dipole or vector recorded by the electrocardiograph.

This equivalent dipole theory assumes that electric potentials at the body surface can be represented at any instant by a single resultant dipole vector.[24] Although oversimplified, this concept is applicable to the

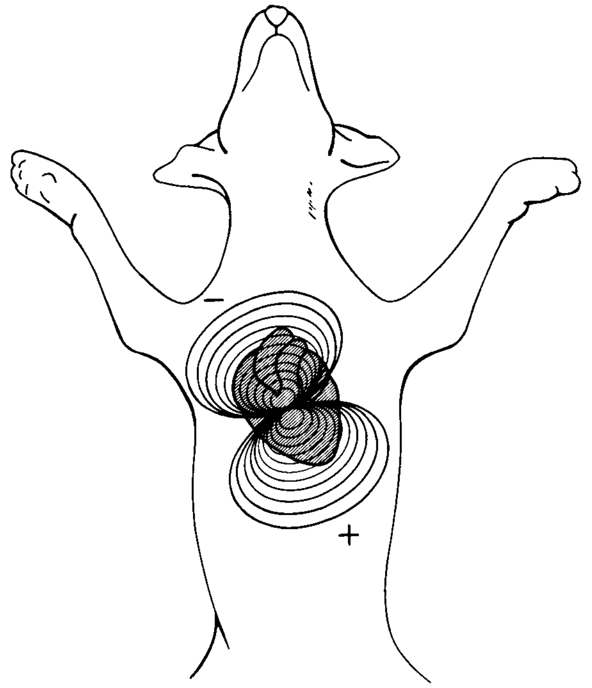


FIGURE 6–8

The electric potential of the heart can be determined at an external point and resolved into a single electric force or vector that acts as a dipole. One half of the dipole or electric field is positive, and the opposite half is negative. When electrodes are attached to the skin on the legs, cardiac electric activity can be recorded by an electrocardiograph. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

surface ECG. The resultant force registered in any given bipolar lead is in direct proportion to the projection of the instantaneous vector on the axis of the lead and is inversely proportional to the cube of the distance between the dipole and each of the lead electrodes. This vector concept was used by Einthoven to determine the mean electric axis of the extremity leads (I, II, III).

The dipole theory has been criticized because heart muscle is anisotropic (i.e., does not conduct homogeneously in all directions). More accurate analyses of body surface potentials utilize the electric field produced from epicardial potentials. Maps describing potential distribution of the body surface (isopotential lines) can be constructed[28] but are not generally used in clinical veterinary settings.

TRANSCRIPTION OF THE ELECTROCARDIOGRAM

Normally, atrial and ventricular contractions are preceded by electric activity that initiates myocyte excitation-contraction coupling[1] (Fig. 6–9). The cardiac impulse originates in the pacemaking cells of the sinus node located at the junction of the cranial vena cava and right atrium. A depolarization (activation) wave spreads through specialized internodal tracts to activate first the right and then the left atrium. The cardiac impulse then slows dramatically while traversing the specialized conduction tissue of the AV node and AV junctional tissue. This delay facilitates more effective synchronized atrial and ventricular contractions. When the impulse emerges from the AV junctional tissue, its velocity increases through the bundle of His, right bundle branch, common left bundle branch, anterior and posterior fascicles of the common left bundle branch, and Purkinje network. The cardiac impulse emerges from the Purkinje network and then spreads by cell-to-cell conduction through ventricular myocytes.[25, 27]

The P wave reflects atrial depolarization and precedes the QRS complex. The Q wave is the first negative wave in the ventricular depolarization complex. The R wave is the first positive wave, and the S wave is the first negative wave following the R wave. Collectively, these waves are called the QRS complex. Ventricular recovery (repolarization) is represented by the T wave.[21]

APPROACH TO ELECTROCARDIOGRAPHY

CLINICAL INDICATIONS

Electrocardiography is clinically useful (1) to diagnose cardiac arrhythmias, (2) as an adjunct to detect cardiac enlargement (dilation or hypertrophy), and (3) to indicate certain electrolyte, acid-base, systemic, or metabolic disorders[20, 21, 28] (Table 6–2).

THE ECG AS PART OF THE CARDIAC DATA BASE

Effective management of arrhythmias (chapters 18 to 20), heart failure (chapter 12), and a variety of systemic and metabolic disorders (chapters 33, 34) requires accurate ECG assessment.[21, 29]

Cardiac lesions do not always cause or correlate with ECG abnormalities. The electrocardiograph may be normal even in the face of advanced cardiovascular disease or heart failure.[30] Other factors may obscure ECG evidence of cardiac chamber enlargement, such as body conformation or the dampening effects of pericardial or pleural effusion or obesity. Moreover, a morphologically normal heart may develop lethal arrhythmias in a variety of disorders (chapter 33).

The ECG may be useful in evaluating animals with

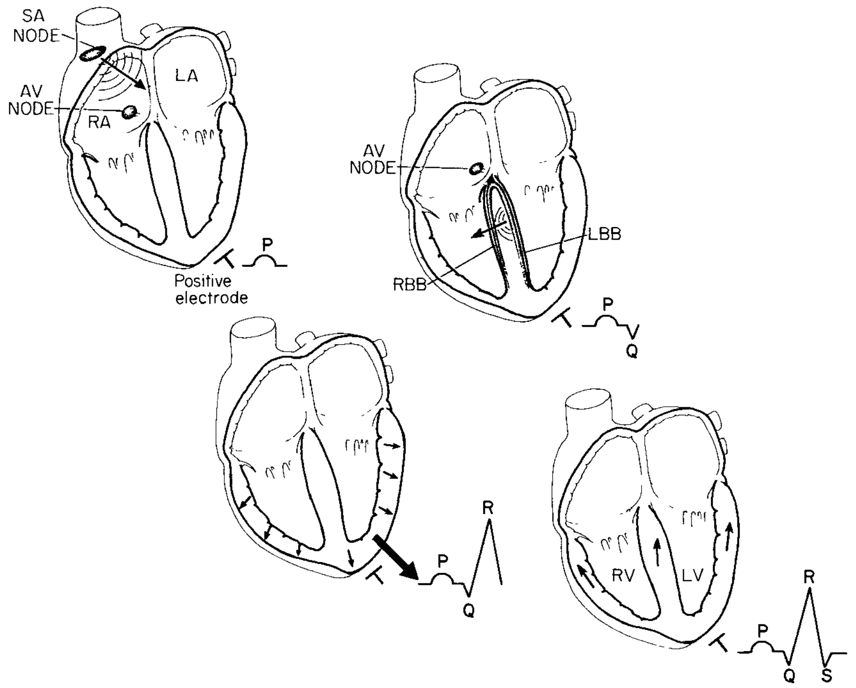


FIGURE 6–9

Sequence of electrical impulse conduction and cardiac chamber activation as it relates to the electrocardiogram. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

metabolic diseases such as endocrinopathies (e.g., hypoadrenocorticism, thyrotoxicosis, pheochromocytoma) or systemic disorders (e.g., shock, neoplasia).[31, 32] Severe electrolyte disorders, acid-base disturbances, or metabolic changes may affect myocyte electrochemical gradients, altering depolarization or repolarization with associated ECG abnormalities. Electrocardiographic alterations in such cases may reflect systemic and not organic heart disease. Thus, it is essential to correlate the ECG with other diagnostic tests.

An ECG is an essential diagnostic step in evaluating heart disease and is required to help individualize therapy. *No animal should be given cardiac medication before evaluation of an ECG.* However, *the ECG has limitations and is only a laboratory test that must be interpreted in conjunction with the entire data base* (i.e., history, physical examination, radiographs, clinical pathology profile, and echocardiogram).[33]

TABLE 6–2
Clinical Indications for Electrocardiography

Arrhythmias
Cardiac monitoring (anesthesia; critical care)
Pacemaker dysfunction
Heart chamber enlargement
Drug effects or toxicities
Myocardial disease
Congenital heart disease
Acquired valvular heart disease
Pericardial disease
Heart failure
Endocrine disorders (e.g., thyrotoxicosis)
Electrolyte imbalance (potassium, calcium)
Acid-base abnormalities
Shock
Dyspnea
Syncope or seizures
Heart murmurs
Gallop rhythms
Cyanosis
Geriatric or presurgical workup
Systemic diseases

LIMITATIONS OF THE ELECTROCARDIOGRAM

The major shortcoming of the ECG is its lack of sensitivity for inferring cardiac chamber enlargement or hypertrophy by changes in the P-QRS-T voltage. In veterinary medicine this problem is complicated by commercial electrocardiographs themselves. These instruments are designed with internal electrical filters intended to prevent artifacts (electrical "noise") from contaminating the desired ECG signal based upon the spectrum of frequencies according to human specifications. The feline ECG, for example, has substantial frequency components at or above 150 Hz in contrast to humans, in whom most of the ECG signal occurs at less than 100 Hz. Commercial electrocardiographs are manufactured to attenuate signals of less than 100 Hz minimally and attenuate signals above 100 Hz maximally. Thus, they significantly attenuate P-QRS-T amplitudes of the feline ECG.[33a] These effects have not been widely investigated in other species.

ANALYZING THE ELECTROCARDIOGRAM

A methodical interpretive approach to the ECG is mandatory to avoid overlooking vital information. The

initial evaluation involves assessing heart rate, rhythm, and mean electrical axis.[21]

CALCULATING HEART RATE

Heart rate should be determined from the lead II rhythm strip. Both atrial and ventricular rates are calculated since they may vary in some arrhythmias. When the basic rhythm is irregular, the ventricular rate can be estimated by counting the number of cycles (R-R intervals) within 3 seconds and multiplying by 20. When the rhythm is regular, heart rate may be calculated as follows:

1. At a paper speed of 50 mm/sec, the width of one small calibration box represents 0.02 sec (see Fig. 6–2). Therefore, the number of small boxes equaling 1 minute is determined by dividing 0.02 sec into 60 seconds, or 3000. Thus, heart rate/minute may be calculated by dividing the number of small boxes within one R-R interval into 3000. At a paper speed of 25 mm/sec, one small calibration box equals 0.04 sec, and heart rate is calculated by dividing the number of small boxes within one R-R interval into 1500.
2. A large calibration box comprises five small boxes. At a paper speed of 50 mm/sec (see Fig. 6–2), it is equal to 0.02 sec times 5, or 0.1 sec; at a paper speed of 25 mm/sec, it equals 0.2 sec. Thus, the number of large boxes equaling 1 minute is determined by dividing 0.1 sec into 60 seconds, or 600. Therefore, the number of large boxes within one R-R interval divided into 600 gives the heart rate per minute at 50 mm/sec paper speed. At 25 mm/sec paper speed, heart rate is calculated by dividing the number of large boxes within one R-R interval into 300.

INTERPRETING CARDIAC RHYTHM

After calculating heart rate, the heart rhythm should then be evaluated. Calipers are helpful for making interval measurements. All recorded leads must be examined for arrhythmias. Rhythm evaluation may proceed as follows:[2, 21, 27]

1. *General inspection* will show whether the tracing shows characteristics of an arrhythmia or represents normal sinus rhythm. If an arrhythmia is observed, one must determine whether it is occasional, frequent, repetitive, regular, or irregular.
2. *Identification* of P waves plays a crucial role in rhythm evaluation. It is important to determine whether the P waves are uniform, multiform, regular, irregular, associated with the QRS complex, or absent.
3. *Recognition* of QRS *complexes* and evaluating their configuration, uniformity, and regularity should then be performed.
4. *Analysis* of the P-QRS *relationship* is the final step. Recognition of P waves is crucial in determining this relationship. Doubling the ECG sensitivity may be helpful to magnify P waves. Precordial chest or esophageal leads may demonstrate P waves that are unrecognizable in other leads. Following calculation of heart rate and analysis of rhythm, all amplitudes, durations, and P-QRS-T intervals are determined from the lead II rhythm strip.

MEASURING THE P-QRS-T COMPLEX

Normal canine and feline ECG values are listed in Table 6–3.[21] Duration of the P wave is measured from its beginning to the end; amplitude is measured from the isoelectric base line to the maximum height of the P wave. The P-R interval is measured from the beginning of the P wave to the beginning of the QRS complex. QRS complex duration is measured from the beginning of the Q wave (if present) or R wave (if no Q wave) to the end of the S wave (if present) or to where the R wave deflection crosses the baseline. The QRS amplitude represents the sum of excursions from the positive R wave and negative S wave. Amplitudes of the Q, R, and S waves are measured from the baseline to the point of their maximal excursion. The S-T interval is the segment between the end of the QRS complex and beginning of the T wave. The Q-T interval represents the distance between the beginning of the Q wave and end of the T wave. Normal canine and feline ECGs are illustrated in Figures 6–10 and 6–11.

MEAN ELECTRICAL AXIS

Einthoven introduced the equilateral triangle concept to help analyze the ECG (Fig. 6–12). Based on three limbs forming the apexes of an equilateral triangle with the heart situated in the center, the sides of the triangle are analogous to standard limb leads (I, II, and III). During ventricular depolarization-repolarization, many dipoles contribute to the electric field and may be represented by a single dipole or vector at any given instant. The mean electrical axis is the average of all vectors that can be projected onto Einthoven's triangle. By transposing the three sides of the triangle so that their centers are superimposed on one another (Fig. 6–13), the triaxial reference system is formed. Adding the unipolar limb lead axes to the triaxial system forms the hexaxial lead system.[21, 33]

The *mean electrical axis* (MEA) refers to the average direction of the electrical potential generated by the heart during the entire cardiac cycle.[26] It is useful for

TABLE 6–3
Normal Values for the Canine and Feline Electrocardiogram

Rate

Dog

70 to 160 beats/min for adult dogs
60 to 140 beats/min for giant breeds
Up to 180 beats/min for toy breeds
Up to 220 beats/min for puppies

Cat

Range: 120 to 240 beats/min
Mean: 197 beats/min

Rhythm

Dog

Normal sinus rhythm
Sinus arrhythmia
Wandering SA pacemaker

Cat

Normal sinus rhythm
Sinus tachycardia (physiologic reaction to excitement)

Measurements (lead II, 50 mm/sec, 1 cm = 1 mV)

Dog

P wave
- Width: maximum, 0.04 second
  maximum, 0.05 second in giant breeds
- Height: maximum, 0.4 mV

P-R interval
- Width: 0.06 to 0.13 second

QRS complex
- Width: maximum, 0.05 second in small breeds
  maximum, 0.06 second in large breeds
- Height of R wave*: maximum, 3.0 mV in large breeds
  maximum, 2.5 mV in small breeds

S-T segment
- No depression: not more than 0.2 mV
- No elevation: not more than 0.15 mV

T wave
- Can be positive, negative, or biphasic
- Not greater than one fourth amplitude of R wave

Q-T interval
- Width: 0.15 to 0.25 second at normal heart rate; varies with heart rate (faster rates have shorter Q-T intervals and vice versa)

Measurements *(Continued)*

Cat

P wave
- Width: maximum, 0.04 second
- Height: maximum, 0.2 mV

P-R interval
- Width: 0.05 to 0.09 second

QRS complex
- Width: maximum, 0.04 second
- Height of R wave: maximum, 0.9 mV

S-T segment
- No marked depression or elevation

T wave
- Can be positive, negative, or biphasic—most often positive
- Maximum amplitude: 0.3 mV

Q-T interval
- Width: 0.12 to 0.18 second at normal heart rate (range, 0.07 to 0.20 second); varies with heart rate (faster rates, shorter Q-T intervals; and vice versa)

Mean Electrical Axis (frontal plane)

Dog

+40 to +100 degrees

Cat

0 to +160 degrees

Precordial Chest Leads (values of special importance)

Dog

CV_5RL (rV_2): T wave positive, R wave not greater than 3 mV
CV_6LL (V_2): S wave not greater than 0.8 mV, R wave not greater than 3.0 mV*
CV_6LU (V_4): S waves not greater than 0.7 mV, R wave not greater than 3.0 mV*
V_{10}: negative QRS complex, T wave negative except in Chihuahua

Cat

CV_6LL (V_2): R wave not greater than 1.0 mV
CV_6LU (V_4): R wave not greater than 1.0 mV
V_{10}: T wave negative; R/Q not greater than 1.0

*Not valid for thin, deep-chested dogs under 2 years of age.
From Tilley LP. Essentials of Canine and Feline Electrocardiography. Interpretation and Management. 3rd ed. Philadelphia, Lea & Febiger, 1992.

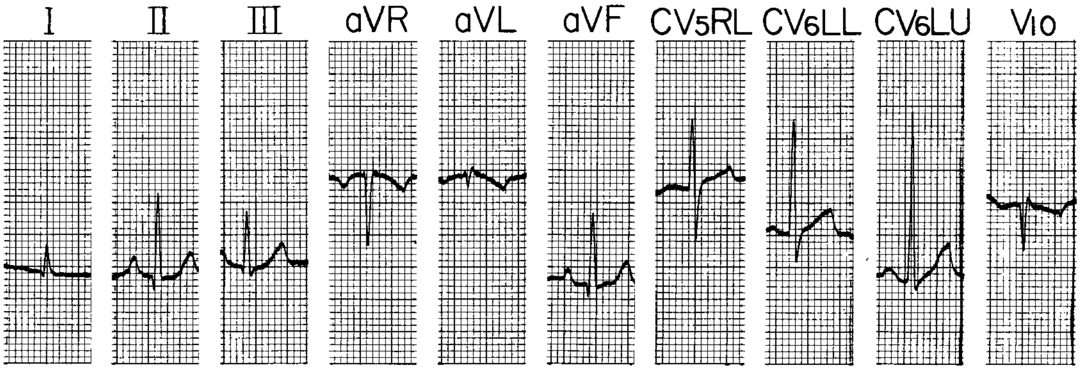


FIGURE 6–10

Normal canine electrocardiogram illustrating the bipolar standard leads (I, II, III), augmented unipolar limb leads (aVR, aVL, aVF), and unipolar precordial chest leads (CV_5RL, CV_6LL, CV_6LU, and V_{10}). Mean electrical axis, +60 degrees. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

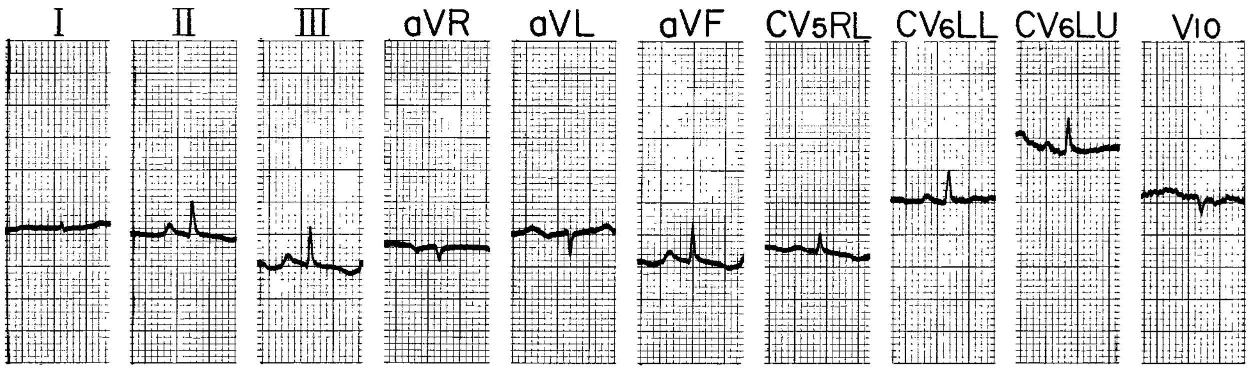


FIGURE 6–11

Normal feline electrocardiogram illustrating the bipolar standard leads (I, II, III), the augmented unipolar limb leads (aVR, aVL, aVF), and the unipolar precordial chest leads (CV_5RL, CV_6LL, CV_6LU, and V_{10}). Mean electrical axis, +90 degrees (isoelectric lead is I). Note the small amplitude voltages, which are normal in the cat. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

suggesting chamber enlargement or intraventricular conduction defects. The MEA may be applied to atrial depolarization (P wave) or ventricular repolarization (T wave). Traditionally, it has been applied to ventricular depolarization (QRS complex). Using the six limb leads and the hexaxial reference system, the MEA in the frontal plane can be calculated. In the normal canine heart, the axis lies between +40 and +100 degrees. In the normal feline heart, the axis lies between 0 and +160 degrees.[21]

There are several methods of determining the MEA. (1) The most accurate (and most time-consuming) involves measuring the net amplitudes in lead I and lead III and plotting these vectors on the triaxial reference system (marked off from the zero point). Perpendicular lines are then drawn from these points to their intersection. A line drawn from the center of the axial reference system to this intersection represents the angle (in degrees) of the QRS axis. (2) Simpler (and less accurate), examine all standard and augmented limb leads and identify the one that is isoelectric (i.e., the algebraic sum of the QRS deflections is zero). The MEA is directed approximately perpendicular to this isoelectric lead toward its net (positive or negative) value.

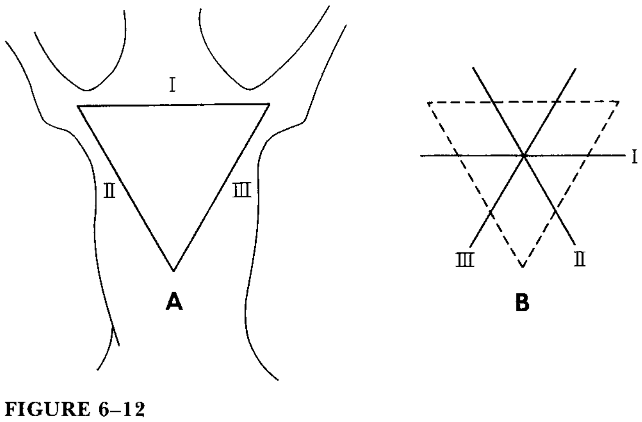


FIGURE 6–12

(A) The equilateral triangle of Einthoven, formed by leads 1, II, and III. (B) The triaxial lead reference system is produced by transposing the three sides of the triangle (leads I, II, III) to a common central point of zero potential. This triaxial lead system is used to formulate the hexaxial lead system. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

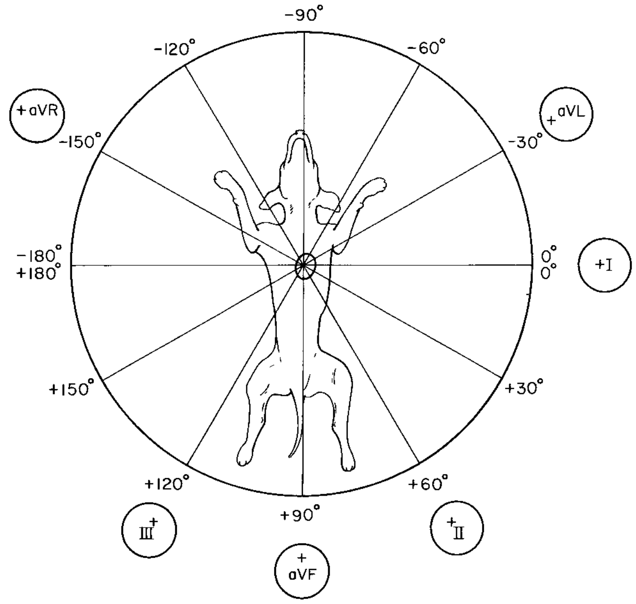


FIGURE 6–13

The hexaxial lead system in Figure 6–12 can be enclosed in a circle and used to determine direction and magnitude of the cardiac electrical axis. The positive pole of each lead is indicated by a small circle. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

THE ABNORMAL ELECTROCARDIOGRAM

The first and most important step in ECG interpretation is differentiating between normal and abnormal waveforms.[21, 27, 29a] One then assesses the various abnormal ECG patterns and correlates them with known structural, physiologic, and hemodynamic conditions. When cardiomegaly is suggested by ECG abnormalities, thoracic radiography, echocardiography, or occasionally angiocardiography may be used for confirmation and further assessment. A simple checklist for ECG evaluation (Table 6–4) and cardiac arrhythmia classification (Table 6–5) may be instructive.

All ECGs depicted here are recorded from *lead II* recorded at a *paper speed of 50 mm/sec* with *amplitude* measured at *1 cm = 1 mV,* unless otherwise noted.

TABLE 6–5
Classification of Cardiac Arrhythmias

- Normal sinus impulse formation
  - Normal sinus rhythm
  - Sinus arrhythmia
  - Wandering sinus pacemaker
- Disturbances of sinus impulse formation
  - Sinus arrest
  - Sinus bradycardia
  - Sinus tachycardia
- Disturbances of supraventricular impulse formation
  - Atrial premature complexes
  - Atrial tachycardia
  - Atrial flutter
  - Atrial fibrillation
  - Atrioventricular junctional rhythm
- Disturbances of ventricular impulse formation
  - Ventricular premature complexes
  - Ventricular tachycardia
  - Ventricular asystole
  - Ventricular fibrillation
- Disturbances of impulse conduction
  - Sinoatrial block
  - Persistent atrial standstill ("silent" atrium)
  - Atrial standstill (hyperkalemia)
  - Ventricular pre-excitation
  - First-degree AV block
  - Second-degree AV block
  - Complete AV block (third-degree)
  - Bundle branch blocks
- Disturbances of both impulse formation and impulse conduction
  - Sick sinus syndrome
  - Ventricular pre-excitation and the Wolff-Parkinson-White (WPW) syndrome
  - Atrial premature complexes with aberrant ventricular conduction
- Escape rhythms
  - Junctional excape rhythms
  - Ventricular escape rhythms (idioventricular rhythm)

ATRIAL AND VENTRICULAR ENLARGEMENT

LIMITATIONS OF ELECTROCARDIOGRAPHY

There is some breed variation in the duration and voltage of P waves and QRS complexes. Often, P waves and QRS complexes may be wider in giant canine breeds than mean values published for dogs in general. Less variation occurs in cats.

The ECG voltage criteria used to infer cardiomegaly have inherent limitations. For example, limb lead and especially precordial lead voltages are influenced by the distance between the electrodes and the heart. Also, voltage criteria may not be as valid for young, emaciated, or narrow-chested animals. Lastly, conditions such as pericardial and thoracic effusions, pneumothorax, obesity, and even the type of commercial electrocardiograph used may reduce the amplitude of QRS deflections recorded at the body surface.

TABLE 6–4
Evaluation of the ECG for Arrhythmias—A Checklist

1. Are P waves present? If not, is there other evidence of atrial activity (flutter or fibrillatory waves)?
2. What is the relationship between atrial activity and QRS complexes?
   a. What are the atrial and ventricular rates?
   b. Is a P wave related to each QRS complex?
   c. Does a P wave precede or follow the QRS complex?
   d. Is the P-R or R-R interval constant?
   e. Are the P-R and R-R intervals regular or irregular?
3. Are the P waves and QRS complexes normal and of similar morphology?
4. Are the QRS complexes wide (greater than 0.05 sec) or normal?
5. Is the ventricular rhythm regular or irregular?
6. Are durations and amplitudes of P, P-R, QRS, and Q-T intervals normal?
7. Are there pauses or premature complexes that require explanation?
8. What is the significance of the arrhythmias in context with the clinical setting?
   a. Is a danger posed by the arrhythmia?
   b. Should attempts be made directly to terminate the arrhythmia?
   c. Can an underlying disorder be corrected, thereby abolishing the arrhythmia?

From Fox PR, Kaplan P. Feline arrhythmias. *In* Bonagura JD (ed). Contemporary Issues in Small Animal Medicine. Vol 7. Cardiology. New York, Churchill Livingstone, 1987, p 251.

RIGHT ATRIAL ENLARGEMENT
(Fig. 6–14; see also Fig. 6–16)

The P wave is increased in both amplitude and duration. Causes include chronic respiratory disease (e.g., chronic bronchitis; collapsed trachea in the dog); certain congenital heart defects (e.g., tricuspid valve dysplasia or stenosis); right ventricular volume overload (e.g., tricuspid regurgitation); and cardiomyopathies.

ECG Characteristics

1. P-wave amplitude is greater than 0.4 mV in the dog (> 0.2 mV in the cat).

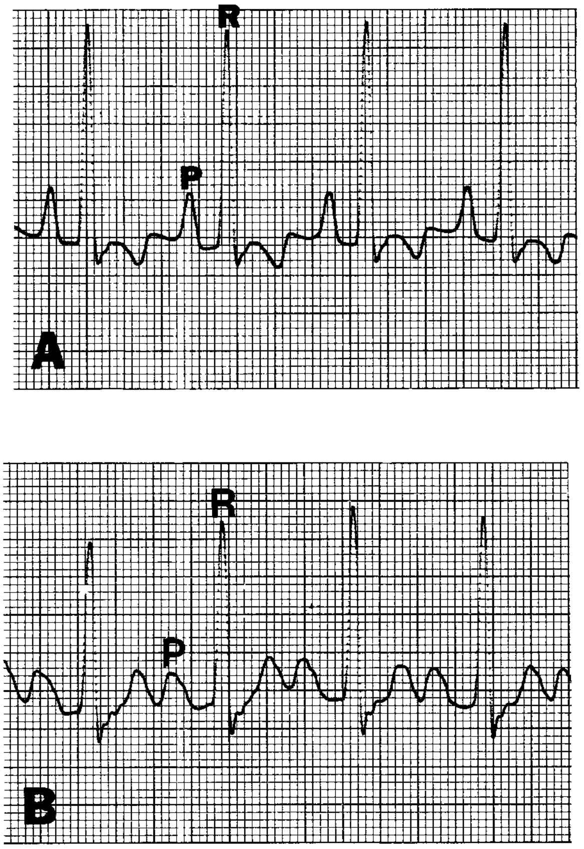


FIGURE 6–14

(A) Biatrial enlargement in a small-breed dog with a collapsed trachea and compensated mitral regurgitation. The P wave is 0.6 mV tall (P pulmonale) and 0.05 sec wide (P mitrale). (B) Left atrial enlargement in a geriatric small-breed dog with chronic acquired valvular disease (mitral insufficiency). P waves are wide (0.075 second), notched, and equivocally tall.

2. P-wave contour is usually tall, slender, and peaked, especially in chronic pulmonary disease (called *P pulmonale*).
3. A slight baseline depression following the P wave is sometimes present; representing atrial repolarization. This T_a wave can also occur with very rapid heart rates.

LEFT ATRIAL ENLARGEMENT

(Fig. 6–14; see also Fig. 6–37)

Causes include left-sided volume overloads from acquired lesions (e.g., canine chronic acquired valvular disease causing mitral regurgitation), or congenital heart defects (e.g., mitral valvular malformations, especially in cats; patent ductus arteriosus; large ventricular septal defect or common atrioventricular canal, especially in cats). Myocardial diseases (especially restrictive and hypertrophic cardiomyopathy in cats and dilated cardiomyopathy in dogs) usually cause atrial enlargement. Left atrial enlargement may also result from other lesions, such as mitral valve stenosis.

ECG Characteristics

1. P waves are increased in duration (called *P mitrale*):
   CANINE—>0.04 second (> 0.05 sec in giant breeds);
   FELINE —>0.04 second (some investigators use a cut-off of 0.035 sec).
2. P wave is often notched (best visualized in lead II) from superimposition of asynchronous right and left atrial conduction. However, P-wave notching by itself is not abnormal unless the P wave is excessively wide.

BIATRIAL ENLARGEMENT

(Fig. 6–14*A*)

Causes include mitral and tricuspid valvular insufficiency, cardiomyopathies, and various congenital heart defects, especially those that occur in combinations. These changes could also occur in right atrial enlargement with an intra-atrial defect or as an interatrial conduction defect in the left atria.

ECG Characteristics

1. P wave is both taller (> 0.4 mV in dogs; > 0.2 mV in cats) and wider (> 0.04 sec in dogs; > 0.05 sec in giant breeds) and cats (> 0.035 to 0.04 sec).
2. P-wave notching or slurring is often present.

RIGHT VENTRICULAR ENLARGEMENT

(Fig. 6–15; see also Fig. 24–6)

Because the ECG does not usually distinguish between ventricular hypertrophy and dilation, the term "enlargement" is preferred. Furthermore, the ECG is a relatively insensitive indicator of right ventricular enlargement. Because of left ventricular dominance during ventricular depolarization, the right ventricle must be markedly enlarged to cause ECG changes. Associated conditions include right-sided pressure overloads caused by certain congenital or acquired diseases including pulmonic stenosis; tetralogy of Fallot; reverse (right to left) shunting in patent ductus arteriosus or septal defect; acquired diseases, including heartworm disease; pulmonary hypertension or embolism; right-sided volume overloads such as tricuspid regurgitation; and, occasionally, severe, chronic pulmonary disease (cor pulmonale) or cardiomyopathies.

ECG Characteristics

CANINE—When any three of the following features are present, right ventricular enlargement is generally diagnosed:

1. S wave in lead CV_6LL greater than 0.8 mV.

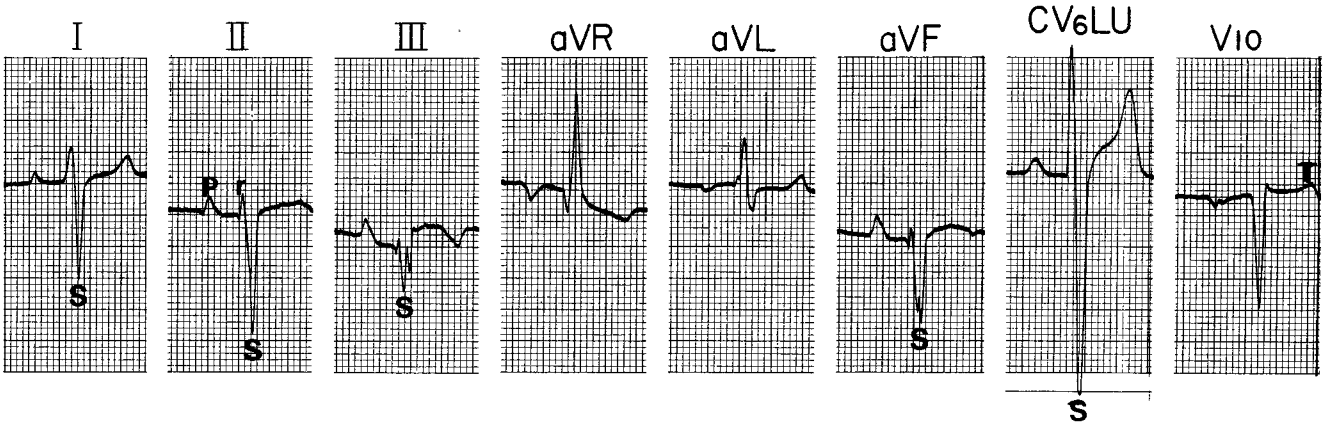


FIGURE 6–15

Severe right ventricular enlargement in a dog with pulmonic stenosis. There is a right axis deviation of approximately −110 degrees. Note the deep S waves in leads I, II, III, aVF, and CV_6LU. The T wave is positive in V_{10}. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

2. Mean electrical axis of the QRS complex in the frontal plane: +103 degrees and clockwise.
3. S wave in lead CV_6LU greater than 0.7 mV.
4. S wave in lead I greater than 0.05 mV.
5. R/S ratio in CV_6LU less than 0.87 mV.
6. S wave in lead II greater than 0.35 mV.
7. S waves present in leads I, II, III, and aV_F.
8. Positive T wave in lead V_{10} (except in the Chihuahua breed).
9. W-shaped QRS complex in lead V_{10}.

FELINE—ECG criteria for right ventricular enlargement are not well established. Right bundle branch block is difficult to differentiate from right ventricular enlargement. Radiographic or echocardiographic absence of right ventricular enlargement supports the ECG diagnosis of a conduction defect. Severe right ventricular enlargement produces some of the same ECG features described for the dog.

ECG Characteristics

1. S waves in leads I, II, III, and aV_F (usually 0.5 mV or greater).
2. Mean electrical QRS axis in the frontal plane greater than +160 degrees and clockwise, especially when comparing serial ECGs.
3. Large S waves in leads CV_6LL and CV_6LU (usually > 0.7 mV).
4. Positive T wave in lead V_{10}.
5. Right atrial enlargement (tall P waves).

LEFT VENTRICULAR ENLARGEMENT

(Fig. 6–16; see also Figs. 6–39, 34–2, and 34–3)

ECG criteria for left ventricular (LV) enlargement may represent LV dilation and/or hypertrophy. The main factor determining ECG voltage is overall muscle mass, not ventricular wall thickness. With LV pressure overload, increased wall thickness occurs in the absence of chamber enlargement (concentric hypertrophy). With volume overload, both wall thickness and cavity size increase (eccentric hypertrophy). ECG voltage changes are generally greater in animals with volume overload than with pressure overload. Several ECG changes are possible as a result of increased muscle mass: (1) increased R-wave height, (2) prolonged QRS complex duration, (3) depressed S-T segment, (4) altered T-wave morphology, and (5) left shift of the mean electrical axis in the frontal plane. Prolongation of the QRS complexes occurs only with severe left ventricular enlargement. An abnormal left axis deviation is not diagnostic by itself for left ventricular enlargement.

Causes of left ventricular enlargement include volume overloads (e.g., mitral or aortic valvular regurgitation, left-to-right shunting from patent ductus arteriosus or atrioventricular fistula); high output states (e.g., hyperthyroidism, chronic anemia); pressure overloads (e.g., aortic stenosis, systemic hypertension); and cardiomyopathies.

ECG Characteristics

1. R wave voltage:
   CANINE (except < 2 years old or deep chest breeds):
   i) R wave greater than 3.0 mV in CV_6LU or CV_6LL.
   ii) Large/giant breeds—R wave in leads II, aV_F greater than 3.0 mV.
   iii) Small breeds—R wave in leads II, III, aV_F greater than 2.5 mV.
   FELINE:
   i) R wave in lead II greater than 0.9 mV.

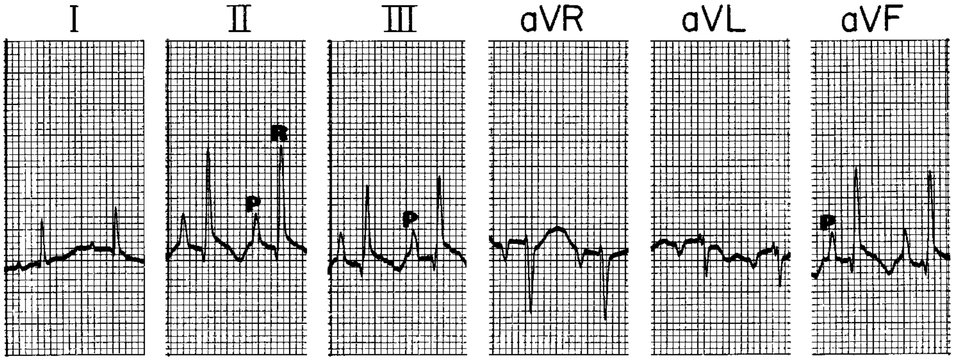


FIGURE 6–16

Right atrial enlargement and left ventricular enlargement in a cat with hypertrophic cardiomyopathy. P waves are tall in leads II, III, and aVF. The R wave amplitude is abnormally tall (1.6 mV in lead II). (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

ii) R wave in leads CV_6LU or CV_6LL greater than 1.0 mV.

2. QRS width:

   CANINE:

   i) Large/giant breeds, QRS greater than 0.06 second.

   ii) Small/medium breeds, QRS greater than 0.05 second.

   FELINE:

   i) QRS greater than 0.04 second (>0.035 by some cardiologists).

3. Displacement of the S-T segment in a direction opposite the main QRS deflection. This causes the S-T segment to sag into the T wave, called S-T segment "coving."
4. Increased T-wave amplitude from repolarization changes.
5. A left shift in mean electrical axis deviation in the frontal plane (< +40 degrees in the dog; < 0 degrees in the cat).

BIVENTRICULAR ENLARGEMENT

Simultaneous enlargement of both ventricles is difficult to confirm accurately by electrocardiography. Diagnosis of right ventricular enlargement is generally unreliable.

ECG Characteristics

1. Precordial chest leads show changes for both right ventricular (deep S waves in CV_6LL and CV_6LU; tall R wave in CV_5RL) and left ventricular (tall R waves in CV_6LL and CV_6LU) enlargement.
2. ECG evidence of left ventricular enlargement with a right shift of the MEA (in dogs).
3. Deep Q waves in leads I, II, III, and aV_F, along with ECG criteria of left ventricular enlargement, may indicate left ventricular enlargement with ventricular septal hypertrophy.
4. ECG criteria for left and right atrial enlargement are often present.
5. ECG may be normal despite severe generalized cardiomegaly.

ABNORMALITIES OF CONDUCTION

SINOATRIAL BLOCK AND ARREST (Fig. 6–17)

With sinoatrial (SA) nodal block, an electrical impulse generated in the SA node is prevented (blocked) from depolarizing the atria. This can be difficult to differentiate from sinus arrest (see Fig. 18–28*D, E*) on the surface ECG, in which impulses are not generated within the SA node. SA block may be caused by various pathologic conditions affecting the atria (e.g., dilation, hypertrophy, fibrosis, necrosis, cardiomyopathy), drug toxicities (especially β-adrenergic blockers, calcium channel blockers, or digitalis glycosides), electrolyte or autonomic imbalances, and other diseases (e.g., sick sinus syndrome). SA block has been described in pug dogs with His bundle stenosis[34] and in patched Dalmatian coach hounds that are born deaf.[35]

ECG Characteristics

1. Variable heart rate depending on the underlying mechanism, with frequent or occasional pauses. SA block is suggested when pauses in the rhythm are precise multiples of normal R-R intervals. Junctional or ventricular escape complexes may occur but can be absent in some conditions (sick sinus syndrome).
2. P waves are usually of normal configuration.
3. The QRS configuration is usually normal.
4. The P-R interval is essentially constant.

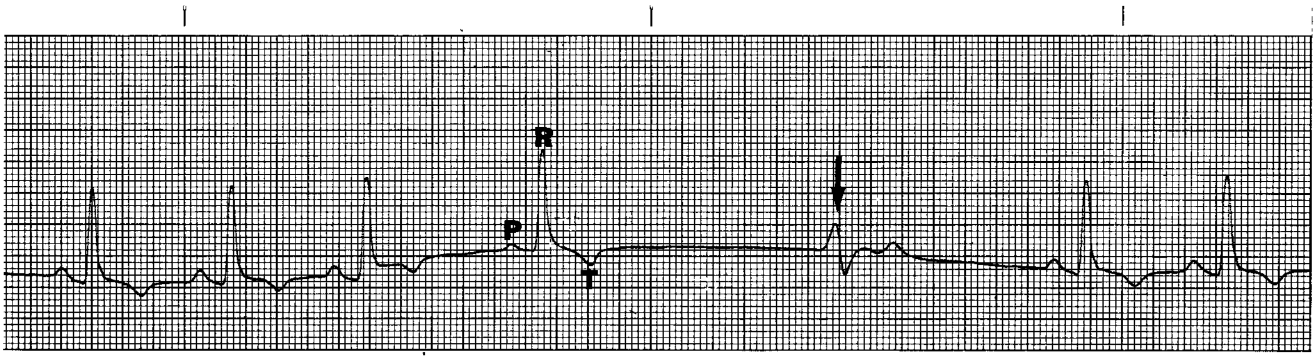


FIGURE 6–17

Sinoatrial block or arrest in a female miniature schnauzer with syncope. Arrow = ventricular escape complex.

PERSISTENT ATRIAL STANDSTILL
(Fig. 6–18)

This arrhythmia is characterized by absence of P waves and a regular escape rhythm with QRS complexes of supraventricular configuration. It may be temporary, persistent, or terminal. Atrial standstill may result from digitalis toxicity or hyperkalemia. Persistent atrial standstill has been associated with various conditions in humans, including muscular dystrophy,[36] and may be hereditary in the English springer spaniel breed.[37, 38] It has been recorded in association with fibrous replacement of atrial myocytes or, occasionally, feline dilated cardiomyopathy. Terminal atrial standstill may occur with cardiac arrest.

ECG Characteristics
(see also following section on hyperkalemia)

1. Slow, regular heart rate (dog—usually <60 beats/min; cat—<160 beats/min.
2. No P waves in any lead (including intracardiac ECG recording).
3. QRS escape rhythm nearly normal in configuration (supraventricular type) or increased duration with bundle branch block pattern.
4. No P waves evident after atropine administration or following exercise.
5. Absent *a* wave (generated by atrial systole) on right atrial pressure recording.

ATRIOVENTRICULAR BLOCK

Atrioventricular (AV) block occurs when conduction of a supraventricular impulse is delayed or interrupted through the AV junction and bundle of His. The precise site of delay cannot be identified from the ECG (bundle of His recordings can delineate the precise site of delay or block but are not performed in a clinical setting). The term "block" should not be used if conduction delay or failure occurs because a supraventricular premature impulse has reached the AV junction or bundle of His too early. The P-R interval represents the time period of impulse conduction from the atria to the ventricles.

First-Degree AV Block
(Fig. 6–19; see also Fig. 19–6*A*)

A prolonged P-R interval may result from certain drugs (e.g., digitalis glycosides, β-blockers, calcium

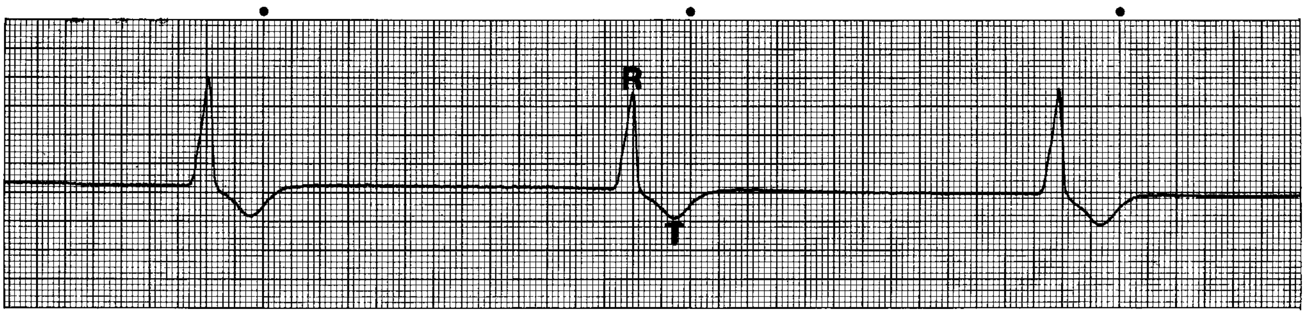


FIGURE 6–18

Persistent atrial standstill in a 4-year-old Siamese cat with clinical signs of dyspnea. No P waves are present; the QRS complexes are increased in voltage and duration, indicating left bundle branch block and/or left heart enlargement. The heart rate is only 40 beats/min. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992.)

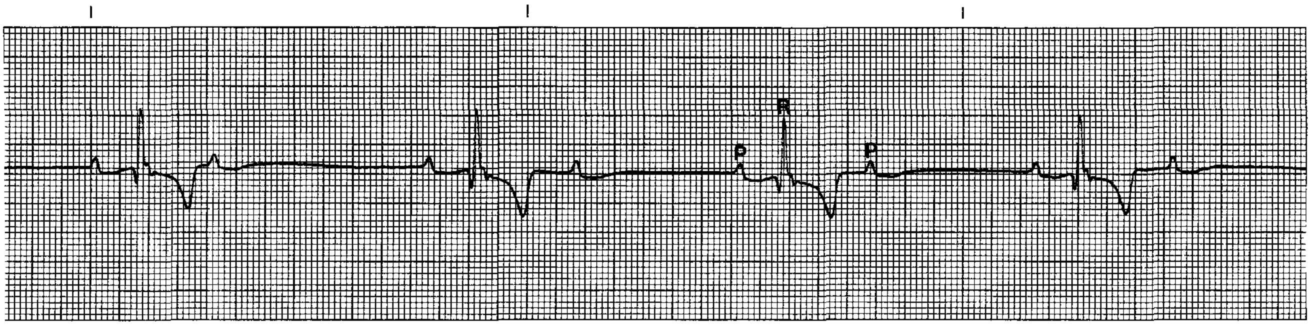


FIGURE 6–19

First-degree and second-degree AV block in a dog with syncope. The P-R interval is prolonged (0.14 second). Every other atrial impulse is conducted (2:1 second-degree block).

channel blockers, occasionally quinidine and procainamide); organic heart disease; age-related degenerative changes in the AV conduction system; hyperkalemia; hypokalemia; vagotonia (often associated with respiratory sinus arrhythmia causing a cyclic increase in the P-R interval); and feline dilated cardiomyopathy. Occasionally, first-degree (1°) AV block may occur in animals that are clinically normal and healthy. The P-R interval tends to shorten with rapid heart rates.

ECG Characteristics

1. P-R interval prolongation:
   CANINE—greater than 0.13 second
   FELINE—greater than 0.09 second
2. Heart rate, rhythm, and P wave are usually normal unless associated with drug intoxication or severe underlying cardiac disease.
3. QRS morphology is usually normal. If bundle branch block is present, 1° AV block may be caused by the conduction delay in the other bundle branch rather than in the AV junction.

Second-Degree AV Block

(Figs. 6–19, 6–20; see also Fig. 19–6*B*, *C*, and Fig. 18–27)

Intermittent failure of AV conduction characterizes 2° AV block. One or more P waves are not followed by QRS-T complexes. A proposed classification takes into consideration the width of the QRS complexes: (1) Type A 2° AV block, with a normal QRS duration (the site of conduction failure is assumed to be above the bifurcation of the bundle of His), and (2) Type B 2° AV block, with a wide QRS (the site of block is assumed to be below the bundle branch bifurcation).

Second-degree AV block may occur in some normal dogs, especially in the early years of life, and in brachycephalic breeds. It is often associated with sinus arrhythmia and other causes of increased vagal tone, or it is physiologic when associated with supraventricular tachycardia. Other associations include microscopic idiopathic fibrosis in older dogs, hereditary stenosis of the bundle of His in pugs, drug effects (e.g., digitalis glycosides; intravenous atropine; xylazine; β-adrenergic blockers; calcium channel blockers), or electrolyte imbalances. In the cat, 2° AV block can occasionally be associated with myocardial diseases and hyperthyroidism.

ECG Characteristics

Mobitz type I (Wenckebach phenomenon) 2° AV block (usually Type A) (Fig. 6–20):

1. The ventricular rate is slower than the atrial rate because of blocked P waves. In the typical form of Wenckebach phenomenon, the rhythm is regularly irregular; the R-R interval becomes progressively shorter as the P-R interval becomes progressively longer until a P wave is ultimately "blocked" (not conducted to the ventricles).
2. P wave is usually of normal configuration.
3. QRS usually normal, indicating that the bundle branches are also normal.
4. Mobitz type I AV block rarely progresses to higher degrees of AV block.

Mobitz type II 2° AV block (usually Type B)(Fig. 6–19; see also Fig. 19–6*B*):

1. The P-R interval is always constant but may be either normal or consistently prolonged. The rhythm is usually regular and suddenly interrupted by the absence of a QRS complex following a P wave. Unlike *Mobitz type I 2° AV block,* no progressive P-R interval prolongation precedes the blocked P wave.
2. There may be a fixed relationship between the atrial and ventricular complexes—e.g., 2:1 2° AV block (two blocked P waves for every one QRS complex), 3:1, 4:1, and so forth. When three or more P waves are blocked, the term "*high-grade* 2° AV block" is used (Fig. 19–6*C*). This frequently deteriorates into complete AV block.

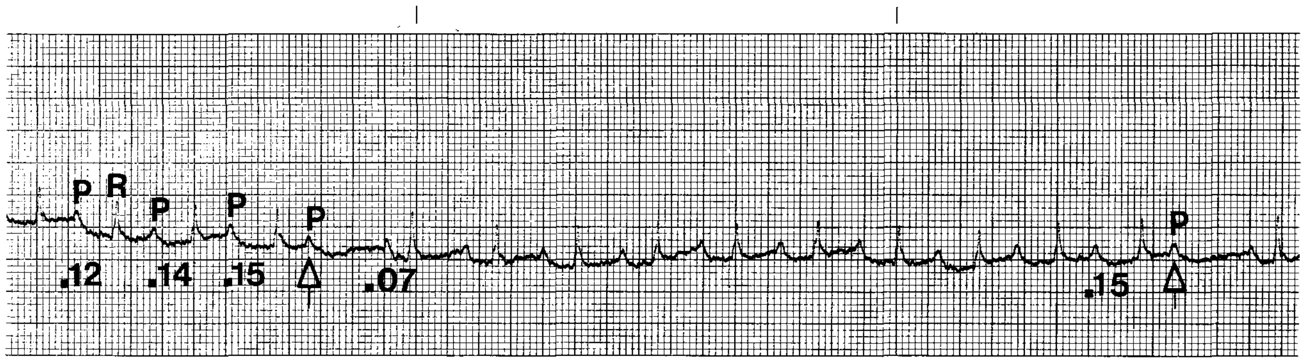


FIGURE 6–20

Mobitz type I second-degree AV block (Wenckebach phenomenon) in a hyperthyroid cat. The P-R interval progressively lengthens until a P wave is not conducted (arrow). (Modified from Fox PR, Kaplan P: Feline arrhythmias. *In* Bonagura JD (ed): Contemporary Issues in Small Animal Practice. Vol 9: Cardiology. New York, Churchill Livingstone, 1987, p 251, with permission.)

3. The ventricular rate is slower than the atrial rate because of blocked P waves.
4. P waves are usually normal.
5. If the QRS complexes are of abnormal configuration, the conduction defect may involve the bundle of His or proximal bundle branches. Mobitz type II AV block (Type B) may progress to higher degrees of AV block.

Complete AV Block
(Fig. 6–21; see also Fig. 19–6*D*)

Complete (3°) heart block occurs when AV conduction is absent. The ventricles are depolarized by pacemakers originating below the area of the block that usually have a greatly reduced rate of discharge. This results in severe bradycardia and decreased cardiac output (recall that cardiac output = heart rate × stroke volume). Clinical signs frequently accompany this bradyarrhythmia, including syncope, episodic weakness, sudden death, and congestive heart failure. Physical examination will indicate variation in first heart sound intensity, intermittent "cannon *a* waves" noted in the jugular venous pulse (caused when the right atrium contracts against a closed tricuspid valve), and variable presence of third and fourth heart sounds.

Associated conditions include isolated congenital AV block; congenital defects such as aortic stenosis and ventricular septal defect; severe drug intoxication (e.g., digitalis glycosides, β-adrenergic blockers, calcium channel blockers); myocardial diseases including infiltrative disorders; bacterial endocarditis; myocardial infarction; and hyperkalemia. Bundle of His lesions have been identified in affected Doberman pinschers and pugs. Degeneration or fibrosis of the AV node and bundle branches has been associated with endocardial and myocardial fibrosis in cats with cardiomyopathy.

ECG Characteristics

1. P waves bear no constant relationship to the QRS complexes.

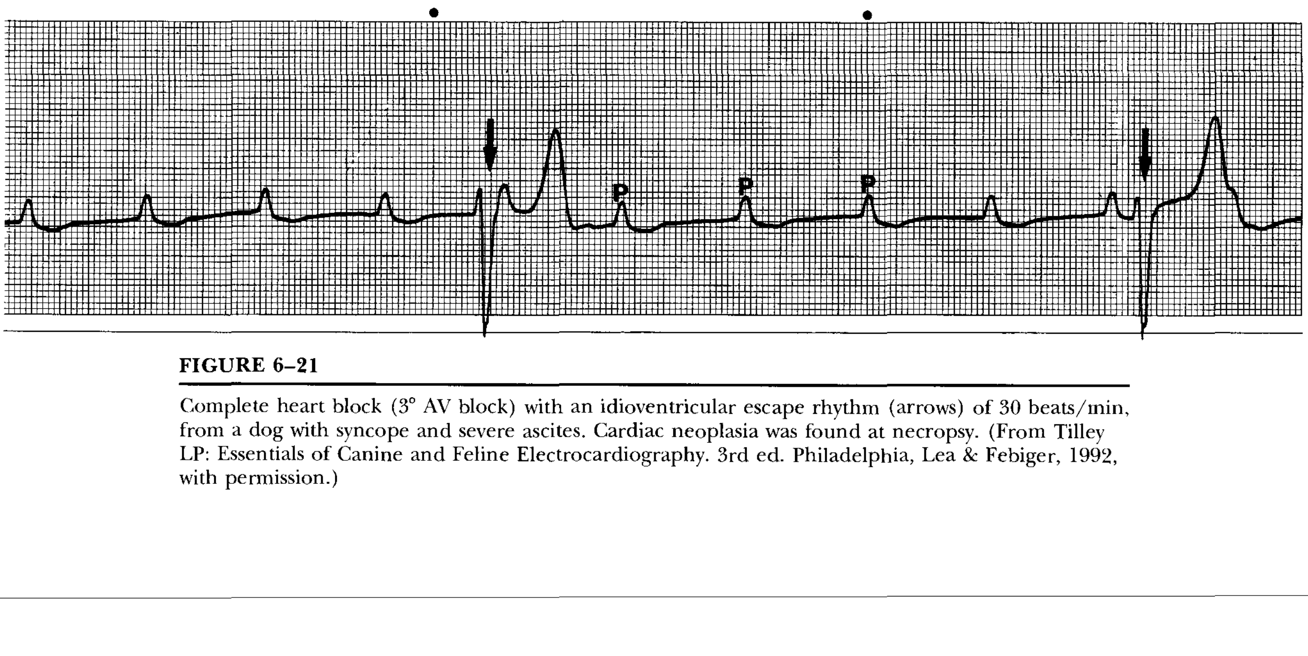


FIGURE 6–21

Complete heart block (3° AV block) with an idioventricular escape rhythm (arrows) of 30 beats/min, from a dog with syncope and severe ascites. Cardiac neoplasia was found at necropsy. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

2. Ventricular rate is slower than the atrial rate (more P waves than QRS complexes).
3. P waves are usually of normal configuration.
4. QRS complexes are usually wide and bizarre when the rescuing pacemaker is of ventricular origin. It is normal when the escape pacemaker is located in the AV junction (above the His bundle bifurcation).

INTRAVENTRICULAR CONDUCTION DEFECTS

The intraventricular conduction system is composed of three major conduction pathways:[25] (1) the right bundle branch, (2) the anterior fascicle of the left bundle branch, and (3) the posterior fascicle of the left bundle branch. A block or delay in conduction can occur in one, two, or all three pathways at the same time. Major forms of intraventricular block include (1) bundle branch blocks (right or left bundle), (2) fascicular blocks (left anterior or left posterior fascicles), (3) combinations of block in the three major conduction pathways (e.g., right bundle branch block with anterior or posterior fascicular block), and (4) block in all three conduction pathways, producing complete (third-degree) AV heart block. Bundle branch or fascicular blocks cause no hemodynamic impairment, unless complete AV block occurs.

Left Bundle Branch Block (LBBB)
(Figs. 6–18, 6–22; see also Figs. 6–37, 6–40, 18–3)

Left bundle branch block (LBBB) results from conduction delay or block in the left bundle branch—either in the main branch or at the level of the anterior and posterior fascicles. This causes a supraventricular impulse to activate the right ventricle first through the right bundle branch. The left ventricle is activated later and more slowly, having to rely on cardiac impulse transmission through myocytes instead of Purkinje fibers. This causes the QRS complex to become wide and bizarre. LBBB usually indicates significant underlying cardiac disease, including cardiomyopathy, congenital subaortic stenosis, certain drug toxicities (e.g., Adriamycin), and severe ischemia.

ECG Characteristics

1. Prolonged QRS complex duration (CANINE—> 0.07 sec; FELINE—> 0.06 sec).
2. Wide and positive QRS complexes in leads I, II, III, and aV_F, and in leads over the left precordium (CV_6LL and CV_6LU).
3. Negative QRS complexes in leads aV_R and CV_5RL.
4. With LBBB, normal initial ventricular septal activation is disturbed, altering the first part of the QRS complex. Thus, the Q wave is often absent in leads that definitely record septal activity in a right-to-left axis orientation (e.g., leads I and CV_6LU).
5. LBBB must be differentiated from left ventricular enlargement. Absence of left ventricular enlargement on thoracic radiographs or echocardiogram lends support to a diagnosis of isolated LBBB.
6. Intermittent LBBB or RBBB may occur that is tachycardia- or bradycardia-dependent; rarely, bundle branch block alternans may occur.

Right Bundle Branch Block (RBBB) (Fig. 6–23)

Right bundle branch block (RBBB) is a delay or block of conduction in the right bundle branch. This results in the right ventricle depolarizing through myocytes by impulses that pass from the left bundle branch to the right side of the septum below the block, instead of through the Purkinje network. This prolonged right ventricular activation causes the QRS complex to become wide and bizarre. The block can occur in the proximal right bundle branch (complete block) or more peripherally in the right bundle branch (incomplete block). RBBB is occasionally found in normal and healthy dogs and cats. It may also be associated with ventricular septal defect, cardiac neoplasia, cardiomyopathy, heartworm disease, and postcardiac arrest.[21] Incomplete RBBB has been found in the bea-

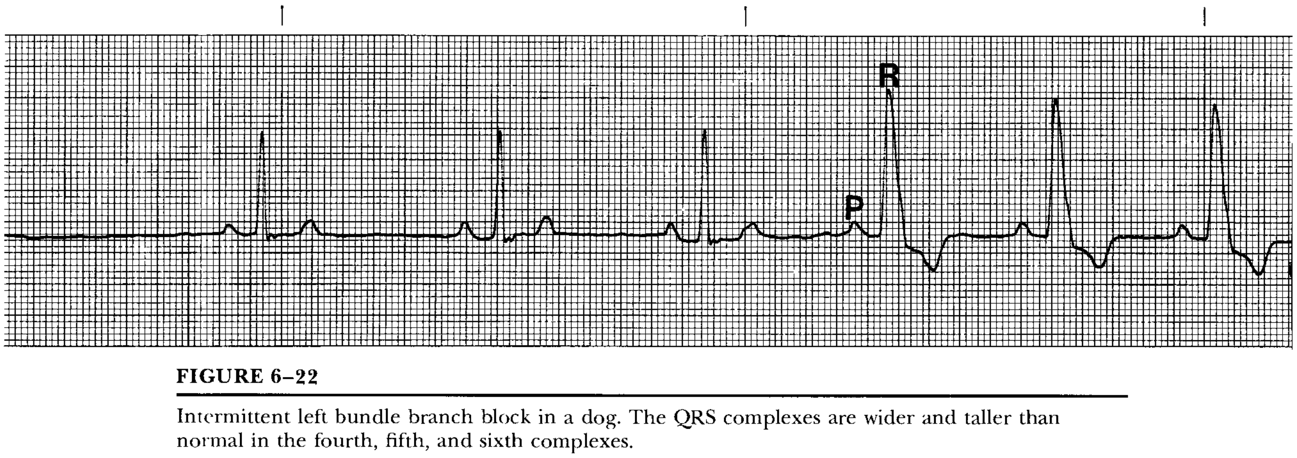


FIGURE 6–22

Intermittent left bundle branch block in a dog. The QRS complexes are wider and taller than normal in the fourth, fifth, and sixth complexes.

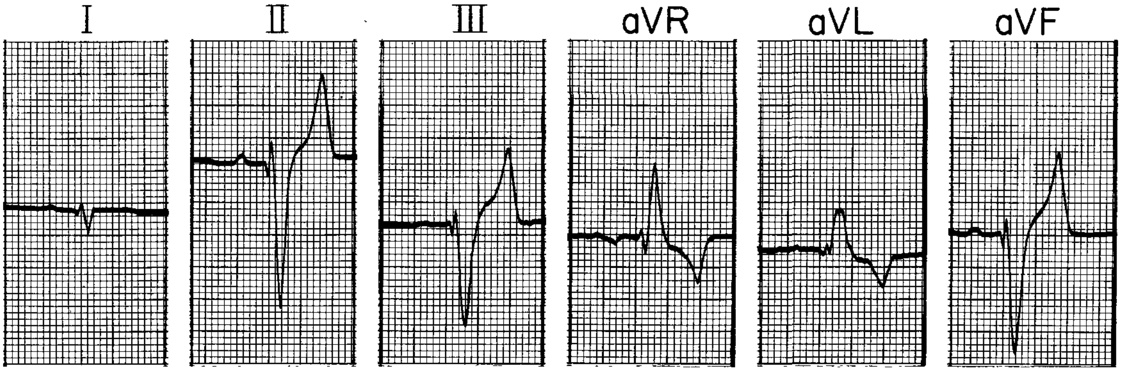


FIGURE 6–23

Right bundle branch block in a dog. The QRS duration is greatly prolonged at 0.09 second. Large and wide S waves are present in leads I, II, III, and aVF. There is a right axis deviation (approximately −90 degrees).

gle[39] as a genetically determined localized variation with right ventricular wall thickness.

ECG Characteristics

Complete RBBB:
CANINE—QRS greater than 0.08 second (>0.07 sec in toy breeds)
FELINE—QRS greater than 0.06 second. Prolonged terminal QRS forces (i.e., S wave)

1. Right axis deviation is usually present.
2. The QRS complex is positive in aV_R, aV_L, and CV_5RL and has a wide RSR′ or rsR′ pattern (often M shaped) in CV_5RL.
3. QRS complexes have large, wide S waves in leads I, II, III, aV_F, CV_6LL, and CV_6LU. An S wave or W pattern is usually present in lead V_{10}.
4. Diagnosis of isolated RBBB is supported if diseases causing severe right ventricular enlargement are excluded. In most cases, the thoracic radiograph or echocardiogram can evaluate right ventricular enlargement.
5. Intermittent RBBB (i.e., tachycardia- or bradycardia-dependent) or bundle branch block alternans may occur.

Incomplete RBBB:
1. When features 1 to 3 above are observed but the QRS duration is within normal limits or slightly widened due to prolonged S-wave duration, incomplete RBBB is suspected.

Fascicular Blocks (Fig. 6–24)

The concept of left bundle branch fascicular blocks (erroneously termed "hemiblock") was promoted by electrocardiographers to clinically apply electrocardiography to conduction system pathophysiology in humans. As classically taught, the anterior and posterior fascicles each pass through the base of the corresponding left ventricular papillary muscles. If the fascicular path to one of these papillary muscles is blocked, ventricular activation begins at the other papillary muscle. This causes the general direction of left ventricular depolarization to shift toward the blocked fascicle and corresponding papillary muscle. In left anterior fascicular block, this results in a marked left axis deviation and only a slight prolongation of left ventricular depolarization.

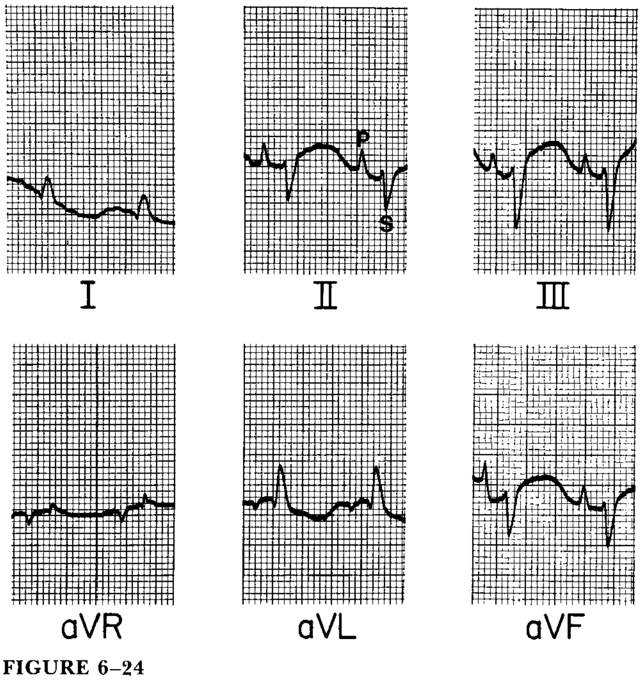


FIGURE 6–24

Left axis deviation suspected due to left anterior fascicular block in a cat with hypertrophic cardiomyopathy. There is a severe left axis deviation (−60 degrees) with a qR pattern in leads I and aVL and an rS pattern in leads II, III, and aVF. Terminal QRS forces are slightly wide, suggesting partial right bundle branch block. (From Tilley LP, et al: Primary myocardial disease in the cat: A model for human cardiomyopathy. Am J Pathol 86:493, 1977, with permission.)

Although the presence of conduction system blocks is acknowledged, much doubt now exists that the ordinary ECG can predict the anatomic locations of interrupted conduction in the left bundle system. This is due to marked anatomic differences in the left conduction system anatomy and inaccuracies of Einthoven's triangle to predict axis changes.[40] In animals, definitive morphologic data are lacking. However, in cats, marked left axis deviation (hypothesized to occur with fascicular block) is often recorded with left ventricular hypertrophic diseases and only rarely in other forms of feline heart disease (chapters 19, 28). Occasionally, a marked left axis deviation can be recorded from apparently normal dogs.

ECG Characteristics of Marked Left Axis Deviation Hypothesized with Left Anterior Fascicular Block

1. QRS complex duration usually within normal limits.
2. Marked left axis deviation in the frontal plane.
3. Small Q wave and tall R wave in leads I and aV_L.
4. Deep S waves in leads II, III, and aV_F.

ECG Characteristics of Right Bundle Branch Block and Marked Left Axis Deviation (Hypothesized with Left Anterior Fascicular Block)

1. QRS complex greater than 0.07 second in the dog; greater than 0.06 second in the cat.
2. Marked left axis deviation in the frontal plane.
3. Wide and deep S waves in leads I, II, III, aV_F, and CV_6LU.
4. Small Q wave and tall R wave in leads I and aV_L.
5. QRS complex in CV_5RL with a wide rsR′ or RSR′ pattern (often M shaped).

VENTRICULAR PRE-EXCITATION AND THE WOLFF-PARKINSON-WHITE SYNDROME

Ventricular pre-excitation is a rare arrhythmia. It occurs when impulses originating in the SA node or atrium activate a portion of the ventricles prematurely through an accessory pathway (Fig. 6–25; see also Fig. 19–5). This accessory pathway enables supraventricular impulses to reach the ventricles initially without going through the AV node (i.e., bypasses all or part of the AV node). The term "Wolff-Parkinson-White (WPW) syndrome" is applied when clinical signs due to paroxysmal supraventricular tachycardia are present.

A variety of anatomic substrates for accessory pathways may exist and result in a number of ECG pre-excitation variations.[41, 42] Three accessory conduction pathways are postulated: bundles of Kent (accessory AV connections), James' fibers (AV nodal bypass tracts), and Mahaim's fibers (nodoventricular tracts). Electrical, radionuclide, and echocardiographic techniques are frequently used in humans to localize the accessory pathway insertion site when surgical or electrical ablation therapy is intended.

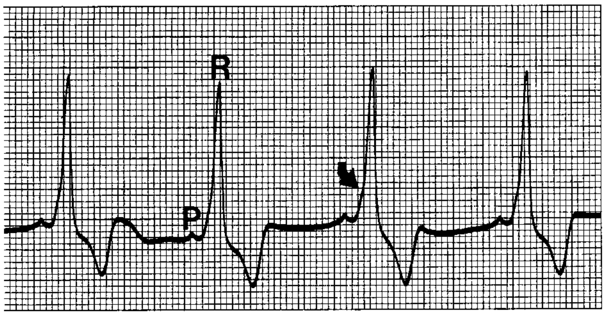


FIGURE 6–25

Ventricular pre-excitation in a dog. A short P-R interval and a widened QRS complex with slurring or notching (arrow) of the upstroke ("delta" wave) are present.

During sinus or atrial impulse propagation, the accessory pathways activate a portion of the ventricles without passing through the bundle of His, while the rest of the ventricle is activated via the normal AV pathway. Pre-excitation of the ventricles results in a shortened P-R interval because the entire impulse is not slowed by normal conduction delay through the AV junction. The QRS complex has a slurred upstroke and is wide because the pre-excitation impulse is conducted through ordinary myocardium without the aid of the specialized conduction system. If the atrial impulse is conducted over the James bypass fibers, a short P-R interval with a QRS complex of normal duration will result (Lown-Ganong-Levine syndrome).

Paroxysmal tachycardia associated with ventricular pre-excitation (WPW syndrome) may occur by the reentry mechanism (chapter 16). An impulse traveling to the ventricles through the AV junction may turn around and re-enter the atria through the accessory pathway. A reciprocal tachyrhythmia is thus established. Drugs are selected that prolong the accessory pathway refractory period (i.e., class 1A and 1C; see chapter 17); in contrast, digitalis may shorten accessory pathway refractoriness and speed the ventricular response with reciprocating tachycardia. In many cases, however, there are no detected arrhythmias or clinical signs.

Ventricular pre-excitation can be congenital with no organic heart disease present; it has been associated with congenital and acquired cardiac defects and hypertrophic cardiomyopathy in cats. In some cases it is idiopathic.[43, 44]

ECG Characteristics

1. P-R interval in ventricular pre-excitation is very short.

2. Heart rate and rhythm are normal in ventricular pre-excitation. In WPW syndrome, the heart rate may be extremely rapid, often greater than 300 beats/min (>400 beats/min in the cat), particularly with 1:1 conduction (P wave for every QRS complex).
3. Sinus P waves are normal in ventricular pre-excitation but difficult to recognize in the WPW syndrome.
4. QRS complex morphology in ventricular pre-excitation is widened with slurring or notching of the R wave upstroke ("delta" wave). The left type (Type A) has predominantly positive QRS complexes in CV_5RL, whereas the right type (Type B) has predominantly negative QRS complexes in CV_5RL. In the WPW syndrome, QRS complex configuration can be normal, wide with a delta wave, or very wide and bizarre.

S-T SEGMENT, Q-T INTERVAL, AND T-WAVE ABNORMALITIES

S-T SEGMENT CHANGES

(Figs. 6–26, 6–39; see also Fig. 24–14)

The S-T segment represents the time from the end of the QRS interval to the onset of the T wave. It may lie above (elevated), at, or below (depressed) the level of the baseline. The baseline or the isoelectric line is on the same level as the T-P segment (between the T wave and the P wave).

S-T segment changes may be attributable to many factors.[21, 45] The magnitude of S-T segment deviation may vary cyclically with changing R-R intervals of respiratory sinus arrhythmia. The degree of S-T deviation increases with shorter preceding R-R intervals in the dog.[46] The S-T segment may display some normal variation in healthy animals. Depressed S-T segment leads with dominant R waves (II, III, aV_F, CV_6LU) can be associated with myocardial ischemia, acute myocardial infarction, electrolyte disturbances, digitalis toxicity, and cardiac trauma. Elevation of the S-T segment (Fig. 6–26) in leads with dominant R waves can be associated with myocardial infarction, pericarditis, and myocardial hypoxia. In addition, ventricular hypertrophy, bundle branch block, and ventricular premature complexes can cause secondary S-T segment changes following abnormalities of the QRS complex. Pseudodepression of the S-T segment due to a prominent T_a wave (atrial repolarization) can occur with tachycardia or pathologic atrial changes.

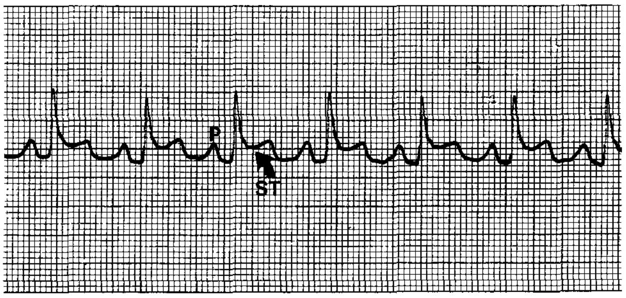


FIGURE 6–26

S-T segment elevation (arrow) in a dog with pericardial effusion.

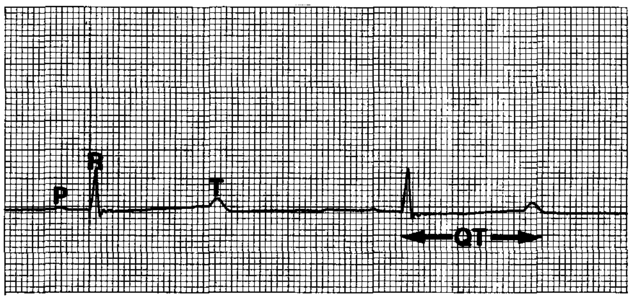


FIGURE 6–27

Lead II rhythm strip recorded from a dog with acute pancreatitis. Sinus bradycardia and Q-T interval prolongation (0.50 sec) are present. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

ECG Characteristics

1. CANINE (magnitude of abnormal S-T segment deviation):
   Depression—0.2 mV or greater; 0.3 mV or greater in lead CV_6LL.
   Elevation—0.15 mV or greater in leads I through aV_F, depression of 0.3 mV in leads CV_6LL and CV_6LU.
   FELINE: Significant S-T segment deviations 0.1 mV or greater.
2. The S-T segment normally curves gently into the proximal limb of the T wave.
3. It is helpful to compare S-T segment changes with previous tracings from the same animal.

Q-T INTERVAL ABNORMALITIES

(Fig. 6–27; see also Figs. 18–25, 33–7, 34–3)

The Q-T interval is measured from the onset of the Q wave to the end of the T wave. It represents the summation of ventricular depolarization. The Q-T interval is dependent on the preceding R-R interval (i.e., the faster the heart rate, the shorter the interval). However, it does not vary with respiratory sinus arrhythmia, probably because fluctuations in canine heart rate occur too slowly to permit resetting of specific ion channels.[47] Drugs that affect the autonomic nervous system can influence the Q-T interval through direct pharmacologic action or indirectly, by changing heart rate. A *prolonged Q-T interval* can occur with

hypocalcemia (see Figs. 18–25, 33–7; 34–3), hypokalemia, quinidine toxicity, ethylene glycol poisoning, strenuous exercise, hypothermia, and central nervous system disorders. A *shortened Q-T interval* can be associated with hypercalcemia (see Fig. 33–7), digitalis toxicity, and hyperkalemia.

Various formulas and tables correlate Q-T interval to heart rate, age, and gender in humans. However, the Q-T interval alone is not very helpful in veterinary diagnostics.

ECG Characteristics

1. The normal range with sinus rhythm:
   CANINE—0.15 to 0.25 second; FELINE—0.12 to 0.18 second.
2. An approximate rule of thumb is that the Q-T interval should be less than one half the preceding R-R interval for a normal sinus heart rate.

T-WAVE ABNORMALITIES (Fig. 6–28)

The T wave is the first major deflection following the QRS complex and represents the ventricular recovery period (repolarization). Its contour may be positive, notched, negative, or biphasic and is most accurately analyzed when compared with T waves from previous ECGs.

T-wave abnormalities may cause abnormal amplitude, shape, or direction (polarity). They can be classified as (1) primary, or changes independent of depolarization, and (2) secondary, or changes directly dependent on depolarization.[48]

T-wave abnormalities can result from myocardial hypoxia, anesthetic complications, and hyperventilation during heat stroke; with heart failure or various heart diseases; during bradycardia (T waves larger) and myocardial infarction (T wave larger with a polarity change). Intraventricular conduction defects such as RBBB or LBBB are often associated with large T waves secondary to the QRS change. T waves become larger and spiked in hyperkalemia and are smaller and biphasic in hypokalemia. Nonspecific T-wave changes are associated with metabolic diseases (e.g., anemia, shock, uremia, hypothyroidism, and fever), drug toxicity (e.g., digitalis, quinidine, and procainamide), and respiratory abnormalities. T-wave alternans can occur from increases in circulatory catecholamines, hypocalcemia, and acute increase in sympathetic discharge.

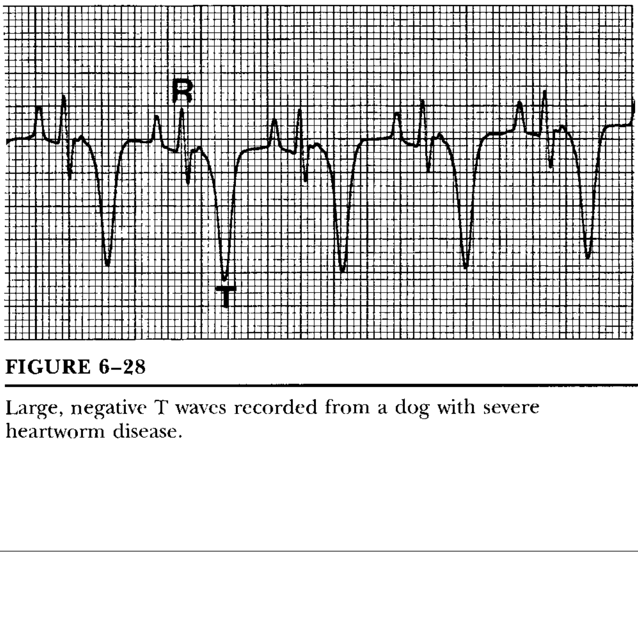


FIGURE 6–28

Large, negative T waves recorded from a dog with severe heartworm disease.

ECG Characteristics

1. T-wave amplitude:
   CANINE—less than 25 percent of the R-wave amplitude.
   FELINE—T wave rarely greater than 0.3 mV and may even exceed the R wave.
2. T-wave morphology: T waves are normally slightly asymmetric and in dogs may be biphasic. They should be positive in dogs greater than 2 years of age and positive in lead CV_5RL; they should be negative in lead V_{10} in all breeds except the Chihuahua. Polarity reversal or a large magnitude in amplitude change on serial ECGs most often represents an abnormal finding. T waves that are sharply pointed or notched are usually abnormal and may indicate acid-base or electrolyte abnormalities (e.g., hyperkalemia).
3. Polarity of secondary T-wave changes is not always equal to that exhibited by the QRS complex.
4. Isolated T-wave alternans (i.e., rhythmic alteration of the T-wave configuration without concomitant change in the QRS complex) can occur and is usually abnormal.

EFFECT OF SELECTED DISEASES ON THE ELECTROCARDIOGRAM

MYOCARDIAL INFARCTION
(Fig. 6–29)

Myocardial infarction is frequently detected in cats at necropsy but is uncommon in the dog.[49] Most cases involve the left ventricle. Microscopic intramural myocardial infarctions (MIMI) and focal areas of myocardial fibrosis are frequent in older dogs with acquired cardiovascular disease. No clinically well-established ECG patterns have been reported to diagnose or precisely localize spontaneous myocardial infarction in the dog, however.

ECG Characteristics

1. Serial ECGs documenting QRS- and ST-T-wave changes provide a higher degree of confidence for

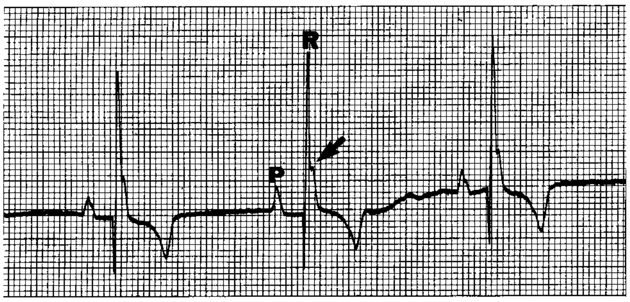


FIGURE 6–29

"Notched R-wave descent" (arrow) recorded from an old dog. This may indicate microscopic intramural myocardial infarction (MIMI). (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

diagnosis of myocardial infarction. The zone of ischemia that surrounds the infarcted region accounts for the S-T segment and T-wave abnormalities.

2. ECG changes that could indicate myocardial infarction:
   a. Sudden S-T segment deviation.
   b. Tall, peaked T waves (first few hours).
   c. Sudden development of Q waves or a change in T-wave direction.
   d. Axis shift in the frontal plane.
   e. Low-voltage QRS complexes.
   f. Sudden development of bundle branch block or AV block.
   g. Sudden onset of ventricular arrhythmias due to ischemia.
   h. Ventricular arrhythmias 12 to 24 hours later due to ischemic effects on the subendocardial Purkinje system.
3. A sloppy R-wave descent (may be associated with MIMI).

HYPERKALEMIA (Fig. 6–30)

The effects of severe, uncorrected hyperkalemia on cardiac conduction and rhythm are often lethal. In severe hyperkalemia, no P wave is recorded because the atrial myocardium does not depolarize. Resultant wide and bizarre QRS complexes may simulate an idioventricular rhythm, but the SA node continues to fire, and its impulses are transmitted via the internodal pathways to the AV junction and ventricles. This is termed a "sinoventricular rhythm."

Changes may not appear on the ECG until serum potassium concentrations are greatly elevated. Moreover, ECG alterations are influenced and potentiated by hyponatremia, hypocalcemia, and acidosis (chapter 33). Therefore, the ECG is not always predictive of serum potassium concentration.

Hyperkalemia is a common clinical condition. It occurs most frequently with feline urinary tract obstruction, oliguric renal failure, hypoadrenocorticism (Addison's disease), and reperfusion injury postaortic thromboembolism.[29, 30, 32]

ECG Characteristics

ECG changes are not directly correlated with precise serum K^+ concentrations, but the following generalizations can be made:

1. Serum K^+ greater than 5.5 mEq/L → T waves larger and peaked.
2. Serum K^+ greater than 6.5 mEq/L → decreased R-wave amplitude; prolonged QRS and P-R intervals; S-T segment depression.
3. Serum K^+ greater than 7 mEq/L → decreased P-wave amplitude; increased P-wave duration; prolonged QRS, P-R, and Q-T intervals.

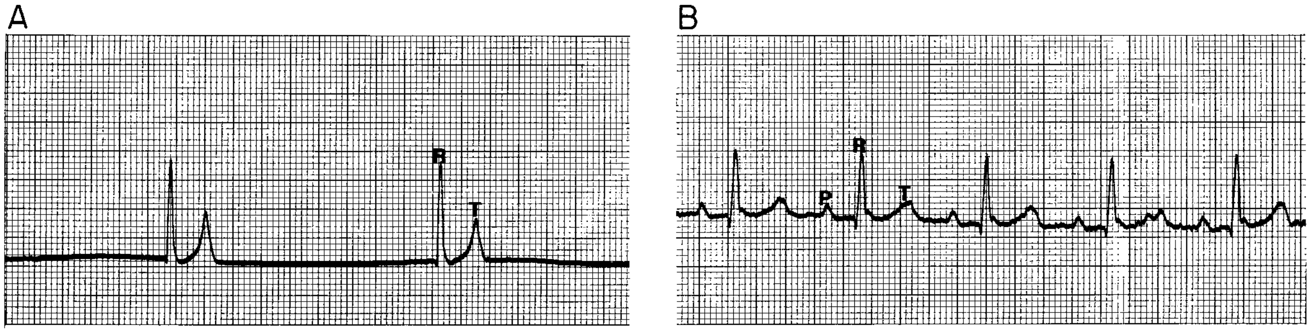


FIGURE 6–30

(A) Atrial standstill recorded from a hyperkalemic dog (serum K^+, 8.4 mEq/L) in hypovolemic shock due to addisonian crisis (hypoadrenocorticism). P waves are absent, and T waves are tall and peaked. (B) After therapy (serum K^+, 4.8 mEq/L), P waves are present, and the QRS-T complex is of smaller amplitude. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

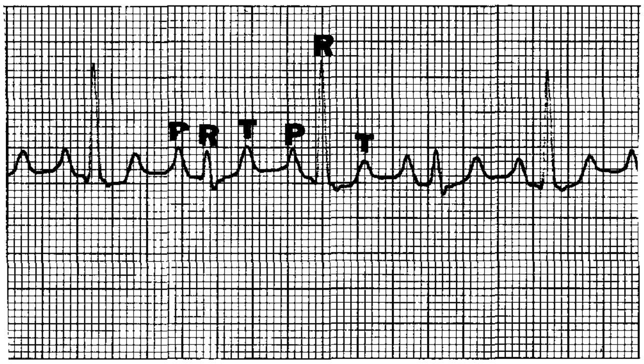


FIGURE 6–31

Electrical alternans in a dog with pericardial effusion. Every other R wave alternates in amplitude.

4. Serum K^+ greater than 8.5 mEq/L → disappearance of the P wave with atrial standstill and resultant sinoventricular rhythm.
5. Serum K^+ greater than 10 mEq/L → increased widening of the QRS complex; eventual replacement of QRS complexes with a smooth biphasic waveform; final stage is ventricular flutter, ventricular fibrillation, or ventricular asystole.

PERICARDIAL EFFUSION AND ELECTRICAL ALTERNANS (Fig. 6–31)

Pericardial effusion is often associated with low voltage complexes, S-T segment deviation, and sometimes *electrical alternans.* The QRS complex amplitude is influenced by many extracardiac factors, such as the distance of the heart from the recording electrode (this distance influenced by chest size, thoracic wall thickness, obesity), presence of emphysema, pneumothorax, or pleural effusion.

ECG Characteristics

1. Decreased QRS amplitude in serial ECGs recorded at different time periods (in the dog, R waves < 0.5 mV in leads I, II, III, and aV_F are suggestive).
2. S-T segment elevation in leads I, II, III, and aV_F, most often seen in acute pericarditis from subepicardial ischemia due to compression by pericardial fluid.
3. P-R segment depression in leads I, II, III, and aV_F, probably representing subepicardial atrial injury.
4. Electrical alternans. This is diagnosed when the P, QRS, or T complexes (or any combination) alter their amplitude every other or every third or fourth beat, and so on. The most common alternating ratio is every other beat and usually involves the QRS complex voltage (i.e., R wave). Shifting cardiac motion of the heart in the pericardial fluid during every other beat causes an alternating shift in the anatomic relationship of the heart to any given electrode. This produces alternating ECG changes.[50]

HYPERTHYROIDISM

(Fig. 6–32; see also Figs. 34–2 and 34–3)

Electrocardiographic abnormalities are common in feline thyrotoxicosis. Sinus tachycardia (greater than 240 beats/min) and increased R-wave amplitude in lead II represent the most common ECG abnormalities. Atrial and ventricular arrhythmias (e.g., atrial premature complexes, atrial tachycardia, ventricular premature complexes, and ventricular tachycardia) and conduction abnormalities are also frequently recorded. Sinus tachycardia, increased R-wave amplitude, and most arrhythmias usually resolve following successful therapy (chapter 34).[51, 51a]

ARRHYTHMIAS

An arrhythmia is an abnormality in the rate, regularity, or site of cardiac impulse origin and/or a disturbance of impulse conduction. During normal sinus

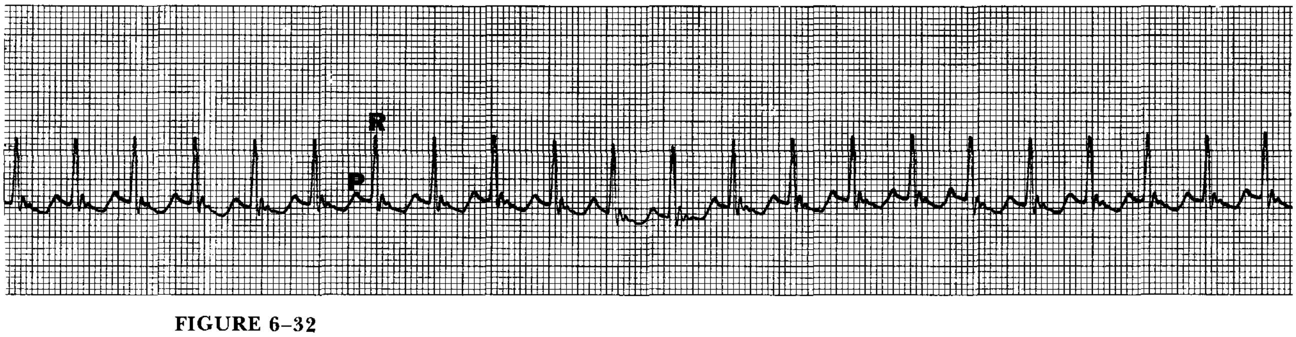


FIGURE 6–32

Sinus tachycardia (285 beats/min) from a cat with hyperthyroidism. The R wave voltage is 1.1 mV, indicating left ventricular enlargement.

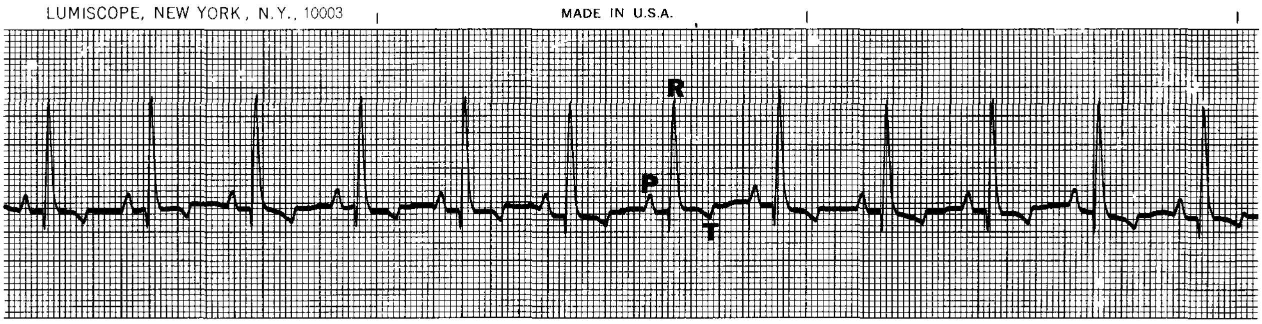


FIGURE 6–33

Normal sinus rhythm in a dog. The heart rate is 165 beats/min. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

rhythm, the cardiac impulse originates in the SA node and spreads in an orderly fashion throughout the atria, AV node and His-Purkinje system, and ventricles. Abnormalities of impulse formation or conduction provide a basis for arrhythmia classification (see Table 6–5) and therapy (chapters 17 to 21).

NORMAL SINUS RHYTHM (Fig. 6–33)

The SA node has a normal inherent pacemaker rate of 70 to 160 beats/minute in the adult dog and approximately 140 to 220 in the adult cat. Sinus rhythm is the most common cardiac rhythm. Rates of SA nodal discharge can become as high as 180 in toy breeds and up to 220 in puppies. A regular sinus rhythm below the normal rate is *sinus bradycardia,* whereas *sinus tachycardia* represents sinus rate above the normal range. An irregular sinus rhythm is called *sinus arrhythmia,* which is common in dogs but uncommon in cats.

ECG Characteristics

1. The rhythm is regular with less than 10 percent variation in R-R intervals. The difference between the largest and smallest R-R interval is less than 0.12 second in the dog; less than 0.10 second in the cat.
2. P waves are positive in lead II with a consistent configuration.
3. QRS complexes are normal. They may be wide and bizarre if atrial enlargement or an intraventricular conduction defect is present.
4. The P-R interval is constant.

ARRHYTHMIAS ORIGINATING IN THE SINUS NODE

Sinus Tachycardia (Fig. 6–32)

Sinus tachycardia can be associated with many conditions: (1) increased sympathetic discharge associated with fright or excitement, (2) a physiologic mechanism in response to increased body metabolism resulting in a greater O_2 demand (e.g., shock); (3) a compensatory mechanism to increase cardiac output (e.g., heart failure); (4) underlying cardiac, systemic, or metabolic disease (e.g., fever, anemia, sepsis, hypoxia, hyperthyroidism); or (5) in response to pharmacologic agents. Sinus tachycardia is the most common arrhythmia in the dog and cat.

ECG Characteristics

1. All criteria of normal sinus rhythm are met except that the heart rate is greater than 160 beats/minute in the dog (above 180 in toy breeds and above 220 in puppies) and greater than 240 beats/minute in the cat.
2. The rhythm is regular, with less than 10 percent variation in R-R intervals and constant P-R intervals.
3. Vagal maneuvers (e.g., ocular pressure) produce only gradual, transient slowing of the heart rate, if any change at all.

Sinus Bradycardia (Fig. 6–34; see also Fig. 19–6A)

Sinus bradycardia represents a regular sinus rhythm slower than the normal sinus heart rate. Severe sinus bradycardia may adversely affect cardiac output and/or increase susceptibility to ectopic cardiac impulse formation. Sinus bradycardia can occur from conditions that increase vagal tone, severe systemic disease, and drug toxicities and certain anesthetics; with feline dilated cardiomyopathy; or during end-stage heart failure. Bradycardia may be a normal ECG variation in the dog, and many large breeds normally have heart rates of 60 to 70 beats/minute.

ECG Characteristics

1. All criteria of normal sinus rhythm are met, except heart rate is less than 70 beats/minute in the dog (< 60/min in large breeds) and less than 120 beats/minute for the cat.
2. The rhythm is usually regular, with a slight variation in the P-P interval.
3. The P-R interval is constant.

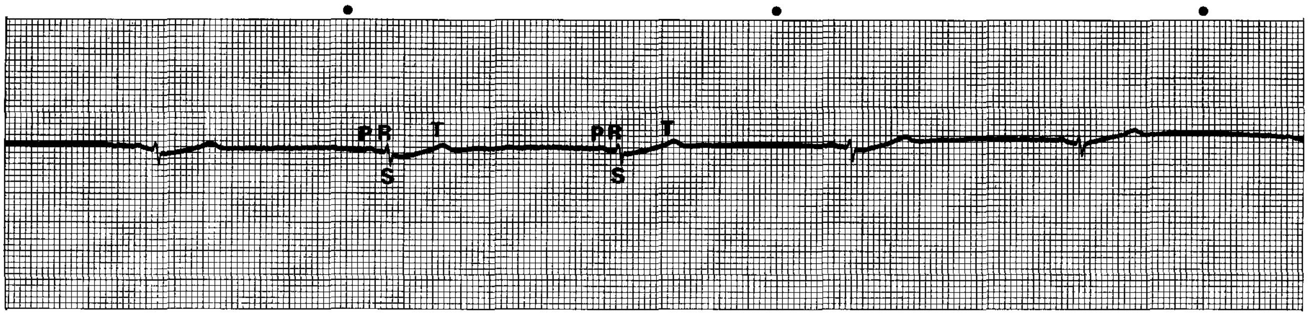


FIGURE 6–34

Sinus bradycardia in a cat (75 beats/min) recorded during surgical anesthetic complications. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

Sinus Arrhythmia (Fig. 6–35)

Sinus arrhythmia is an irregular sinus rhythm originating in the SA node. It is represented by alternating periods of slower and more rapid heart rates, which is usually related to respiration. In *respiratory* sinus arrhythmia, inspiration causes reflex inhibition of vagal tone, resulting in cyclical P-P interval shortening and an increasing heart rate; expiration causes P-P interval lengthening and a slowing heart rate. Respiratory sinus arrhythmia is a frequent normal finding in dogs, especially brachycephalic breeds in which large airway obstruction increases the force of inspiration. Sinus arrhythmia is accentuated by vagal maneuvers such as carotid sinus massage and ocular compression. Atropine will usually eliminate sinus arrhythmia, indicating vagal origin. In cats, sinus arrhythmia is uncommon. When present it is usually associated with upper respiratory infections. *Nonrespiratory* sinus arrhythmia is not associated with respiration.

ECG Characteristics

1. All criteria of normal sinus rhythm are met. In the dog, 0.12 second or greater variability exists between successive P waves, or greater than 10 percent variability exists between R-R intervals. In the cat, 0.10 second or greater variability occurs between successive P waves.
2. P waves, QRS complexes, and P-R intervals are normal.
3. A *wandering pacemaker* is often present. This is a shift of pacemaker discharge from within the SA node or from the SA node to the AV node. Consequently, the direction of atrial depolarization (and P-wave contour) may change. Thus, a wandering pacemaker causes an irregular supraventricular rhythm with changing P-wave morphology. It is usually a normal variation in the dog.

Sinus Arrest (see Figs. 6–17 and 6–40)

Sinus arrest represents failure of SA nodal impulse formation caused by depressed automaticity. Differentiating between SA block or arrest by standard surface ECG is difficult. Prolonged periods of sinus arrest may cause episodic weakness or syncope when subsidiary escape pacemakers fail to discharge.

Intermittent sinus arrest can be a normal incidental finding in brachycephalic breeds, in which it is associated with vagotonia accompanying accentuated respi-

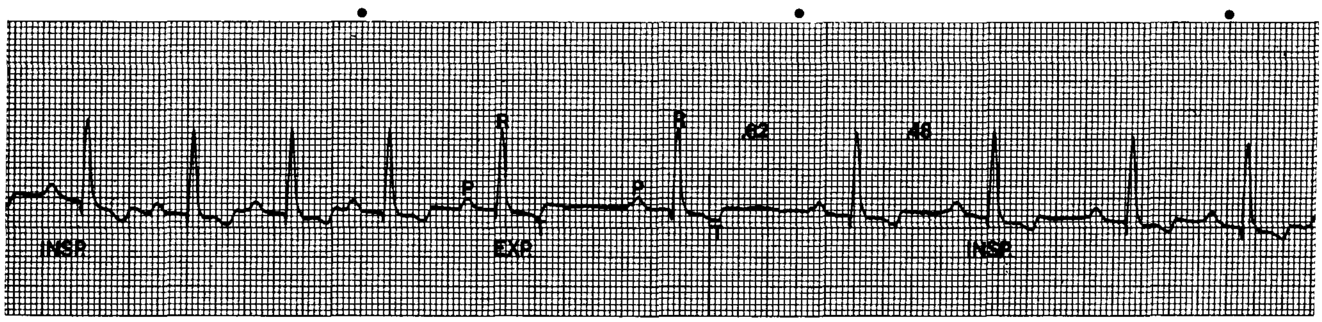


FIGURE 6–35

Respiratory sinus arrhythmia in a dog with an average rate of 120 beats/min. The R-R intervals vary more than 0.12 second as the rate changes with inspiration (INSP) and expiration (EXP). (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

ration. It is rare in the cat. Ocular or carotid sinus pressure often produces sinus arrest or block. Other causes of vagotonia, including surgical manipulation and thoracic or cervical neoplasms, may cause sinus arrest or block.

ECG Characteristics of Sinus Arrest with Normal Sinus Rhythm

1. The heart rate can be variable, depending on the underlying mechanism. The rhythm is regularly irregular, or irregular with pauses demonstrating a lack of P-QRS-T complexes. The pauses are equal to or greater than twice the normal R-R interval.
2. P waves are usually of normal configuration but may vary in shape if a wandering pacemaker is present.
3. QRS configuration is normal unless an intraventricular conduction defect exists.
4. The P-R interval is essentially constant.

Sick Sinus Syndrome (Fig. 6–36)

A number of SA nodal abnormalities are described under this terminology, including severe sinus bradycardia with pronounced SA block, and sinus arrest.[52] When paroxysms of recurrent supraventricular tachycardia (e.g., atrial fibrillation or atrial tachycardia) coexist with this bradyarrhythmia, the term "bradycardia-tachycardia syndrome" is applied. This has been reported in miniature Schnauzers[53] most commonly, but also pugs, dachshunds, cocker spaniels, and mixed-breed dogs can be affected. The condition is rare in felines.

Most dogs with sick sinus syndrome also have coexisting dysfunction of the AV junction or bundle branches or both. Automaticity of lower pacemakers is often depressed. Thus, during long periods of SA block or arrest, latent alternate pacemakers fail to depolarize, causing long intervals of sinus pause (asystole). Syncope may result.

The clinical manifestations of sick sinus syndrome are variable. Some dogs are asymptomatic. Syncope and episodic weakness are the most common clinical signs associated with the bradycardia-tachycardia syndrome. Very occasionally, heart rates may be so slow as to reduce cardiac output and exacerbate cardiac failure.

ECG Characteristics

1. Severe and persistent sinus bradycardia not induced by drugs.
2. Short or long sinus pauses (SA block/arrest) with or without escape rhythms.
3. Atrial fibrillation with a slow ventricular rate (in the absence of cardioactive drugs), usually associated with accompanying disease of the AV junction.
4. Long sinus pause following an atrial premature complex.
5. AV junctional escape rhythm (with or without slow and unstable sinus activity).
6. Bradycardia-tachycardia syndrome: periods of severe sinus bradycardia alternating with ectopic supraventricular tachycardias (atrial tachycardia, atrial fibrillation, or atrial flutter); absence of intervening escape rhythm during long periods of sinus pause.

Tests for SA node dysfunction include the following:

1. Ocular or carotid sinus massage (vagal maneuvers) may cause prolonged periods of sinus arrest (> 3 sec). Increased vagal tone may partially contribute to this syndrome.
2. Atropine (0.015 to 0.04 mg/kg IV) fails to cause a marked increase in heart rate (normally at least a 50 percent increase occurs), indicating that the SA node dysfunction is not due to excessive vagal tone.
3. Simultaneous automatic monitoring with radiotelemetry and time-lapse video recordings have been used to correlate syncope with arrhythmias.
4. After cessation of rapid right atrial pacing, the atrium can fail to depolarize for as long as 15 seconds (normal in the dog is 1.5 sec).

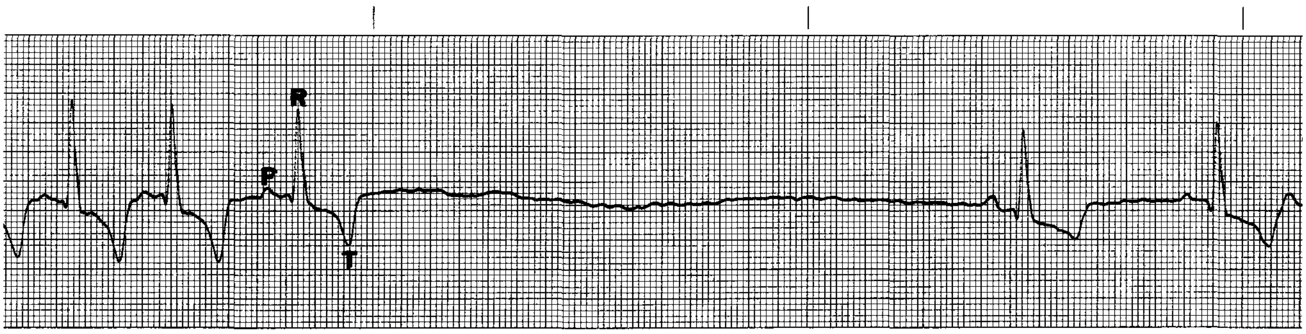


FIGURE 6–36

Prolonged ventricular asystole due to sinoatrial block or arrest after a vagal maneuver (ocular pressure) was performed on a dog with sick sinus syndrome. No escape beats occur during this interval.

5. Failure of sinus rhythm initiation after electric cardioversion of tachycardia.

DISTURBANCES OF ATRIAL RHYTHM

Atrial Premature Complexes

(Fig. 6–37; see also Figs. 6–47, 18–1, 18–2*F*, 18–3, 19–2)

Atrial premature complexes (APCs) can originate from any area in the atria or AV node. Although APCs are occasionally detected in clinically normal dogs and cats, they are usually associated with structural cardiac, metabolic, systemic, or inflammatory diseases. Isolated or infrequent premature atrial complexes cause no hemodynamic or electrical instability and require no therapy. They may occasionally precipitate or presage the occurrence of supraventricular tachyarrhythmias such as atrial tachycardia or flutter. Causes of APCs include atrial enlargement from volume overloads (e.g., congenital or acquired valvular regurgitation, or left-to-right shunting congenital heart diseases), myocardial diseases (idiopathic or secondary to systemic or metabolic diseases), sepsis, neoplasia (especially hemangiosarcoma), hyperthyroidism, and drug toxicity (e.g., digitalis glycosides, general anesthesia).

ECG Characteristics

1. A premature, ectopic P′ wave (called P′ wave) occurs and has a different configuration from normal sinus P waves. The P′ wave may be negative, positive, biphasic, or superimposed on the previous T wave.
2. A premature QRS complex with a configuration similar to that of sinus-initiated complexes follows the P′ wave.
3. If the P′ wave occurs too early relative to the preceding T wave, the AV node may not have recovered adequately to permit conduction of the P′ wave impulse to the ventricles. A nonconducted P′ wave results (QRS is absent).
4. Cardiac rhythm is irregular due to the premature P′-QRS-T complexes that disrupt the normal sinus-initiated rhythm.
5. If there is partial recovery of the AV node or the intraventricular conduction system, the P′ wave is conducted with a long P′-R interval or with a change in the normal QRS configuration (called aberrant conduction).
6. The P′-R interval is usually equal to or greater than the sinus-initiated P-R interval.
7. A *noncompensatory pause* may result. It is recognized when the R-R interval of the two normal sinus complexes that enclose the APC is less than the R-R intervals of three consecutive sinus complexes. This is caused by retrograde conduction of the APC into the SA node, which discharges the SA node prematurely, resetting SA nodal discharge and, thus, timing of the normal sinus rhythm.

Atrial Flutter (Fig. 6–38; see also Figs. 18–10 and 18–11)

Atrial flutter is an uncommon tachyrhythmia characterized by a rapid atrial rate usually exceeding 300 beats/minute, and with variable ventricular conduction. In the classic form, normal P waves are replaced by "sawtooth" waves (called **F** waves). Varying degrees of AV conduction are usually present. When 1:1 atrial to ventricular conduction occurs, the arrhythmia may be difficult to distinguish from atrial tachycardia.

Atrial flutter is associated with conditions that cause other atrial arrhythmias (especially diseases producing severe atrial enlargement), ventricular pre-excitation (WPW syndrome), and, occasionally, feline restrictive or hypertrophic cardiomyopathy.

ECG Characteristics

1. Normal P waves are replaced by sawtooth flutter waves (**F** waves), which represent a combination of ectopic and pronounced atrial repolarization waves.
2. The atrial rhythm (**F** waves) is regular and rapid

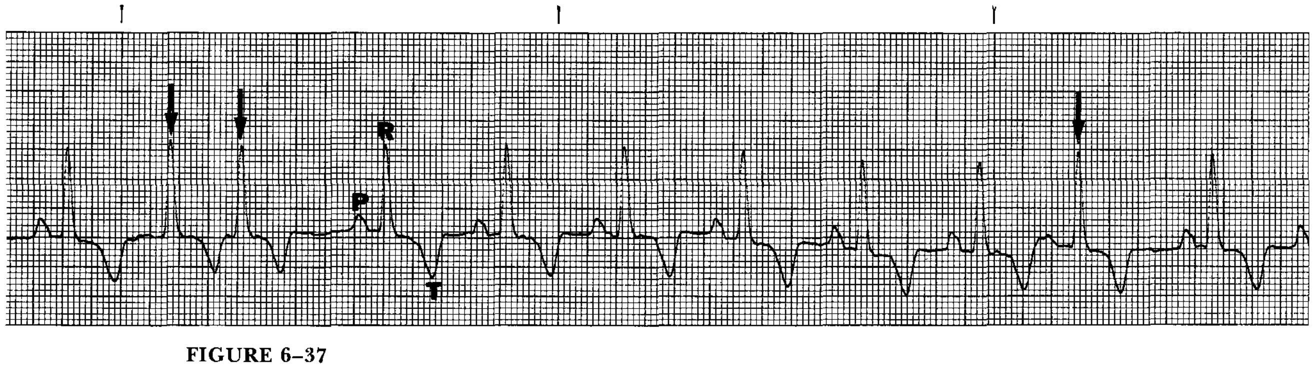


FIGURE 6–37

Atrial premature complexes *(arrows)* and P mitrale in a dog with congestive heart failure caused by chronic mitral regurgitation.

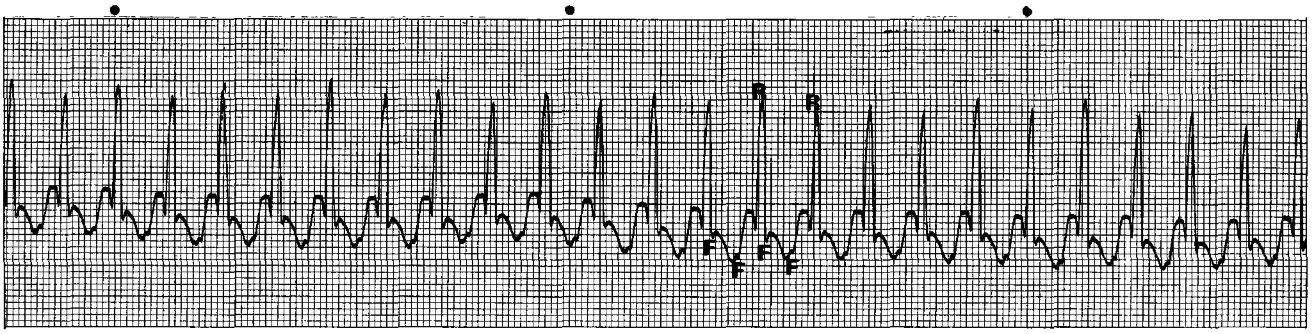


FIGURE 6–38

Atrial flutter with 2:1 conduction (ventricular rate, 330/min) from a dog with an atrial septal defect. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

(usually > 300 beats/min). The ventricular rhythm and rate depend the state of AV conduction and atrial rate. When the rate of atrial and ventricular depolarizations is equal, 1:1 atrioventricular conduction is said to be present; when two atrial depolarizations occur for each QRS-T complex, conduction is said to be 2:1, and so on.

3. The QRS configuration is normal, or wide and bizarre due to bundle branch block, aberrant ventricular conduction, or ventricular pre-excitation.
4. When conduction through the AV node is constant, the interval between the QRS complex and the **F** wave is of constant duration. This interval may vary based on changing conduction and second-degree AV block.

Atrial Fibrillation (Fig. 6–39; see also Figs. 18–2, 18–12, 18–13, 19–4, and 22–1)

Atrial fibrillation is common in the dog but uncommon in the cat. Although it can be paroxysmal, it is more usually sustained. The loss of atrial contribution to ventricular filling, combined with a rapid ventricular heart rate, may substantially reduce cardiac output and exacerbate heart failure. Atrial fibrillation is usually associated with severe atrial enlargement. In dogs, it most often results from dilated cardiomyopathy, severe chronic mitral regurgitation, or uncorrected congenital heart diseases such as patent ductus arteriosus.[54] Additional causes include ventricular pre-excitation (WPW syndrome) and, rarely, severe systemic or metabolic diseases (e.g., hypoadrenocorticism, gastric torsion-volvulus). Occasionally, atrial fibrillation may occur in large or giant-breed dogs without cardiac enlargement. In cats, atrial fibrillation is predominantly associated with hypertrophic or restrictive cardiomyopathy.[54–56]

ECG Characteristics

1. Discernible P waves are absent. In coarse atrial fibrillation, large oscillations (called "f" waves) of varying amplitude replace the normal sinus P waves. When prominent f waves resemble atrial flutter, the term "atrial flutter-fibrillation" is used.
2. Ventricular heart rate is rapid and irregularly irregular (rarely, a slow ventricular rate is present).
3. The QRS configuration is normal, or more commonly, widened owing to bundle branch block or aberrant conduction. Normal QRS complexes

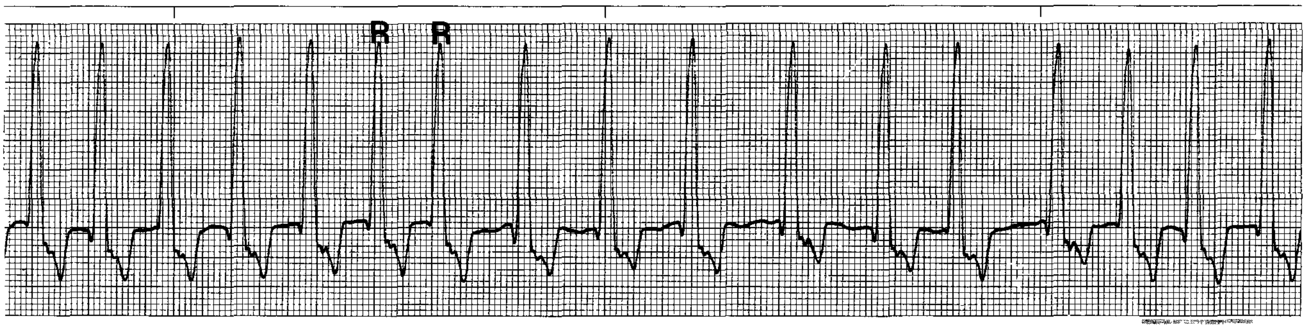


FIGURE 6–39

Atrial fibrillation recorded from a dog with congestive heart failure. The heart rate is rapid and irregularly irregular. P waves are absent. The tall and wide QRS complexes indicate left heart enlargement. The S-T segment is depressed.

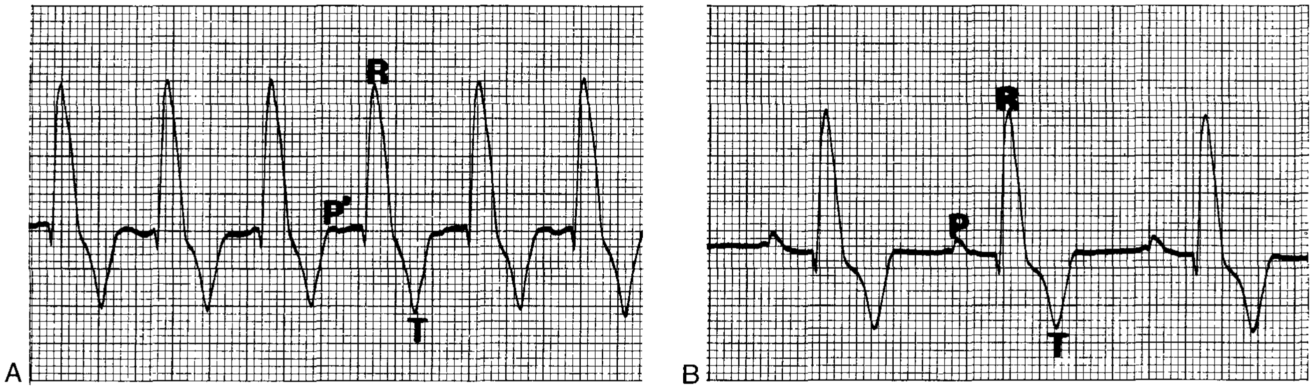


FIGURE 6–40

(A) Supraventricular tachycardia, probably atrial tachycardia, recorded from a dog. The ectopic origin cannot be identified with accuracy in this strip. (B) After vagal maneuvers (ocular pressure), the tachycardia has been terminated. The configuration of these sinus QRS complexes is the same as in strip A and represents a left bundle branch block configuration. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

sometimes vary in amplitude, especially during rapid heart rates.

4. The ventricular rate is irregularly irregular because the AV junction conducts only a limited number of fibrillatory waves to the ventricles in a sporadic fashion.

SUPRAVENTRICULAR TACHYCARDIAS
(Figs. 18–2, 18–4, 18–8, 18–9, 18–14 through 18–17)

Nomenclature

Tachyarrhythmias are sometimes differentiated as to whether the QRS complexes are narrow (i.e., normal width) or wide. *Narrow QRS tachycardia* represents complexes less than 0.065 second wide in the dog and less than 0.045 second in the cat. These complexes indicate that atrioventricular conduction occurs via the AV node. A variety of electrophysiologic mechanisms can account for tachycardias originating in the atria or AV junction with ECG characteristics of a supraventricular QRS complex, regular R-R interval, and no evidence of ventricular pre-excitation. These tachycardias have been termed *paroxysmal atrial tachycardia* if the P wave occurred in front of the QRS, and *paroxysmal junctional (or nodal) tachycardia* if the P wave exhibited retrograde contour and occurred within or just following the QRS complex. A broader, generalized term, "paroxysmal supraventricular tachycardia," is frequently applied to encompass this group. The term "reciprocating tachycardia" has been substituted when the mechanism is thought to be re-entry. It must be remembered that some cases of supraventricular tachycardia can have wide QRS complexes because of pre-existing or functional bundle branch block or conduction through an accessory AV pathway.[30, 48] In this chapter, descriptive titles are applied for the sake of clarity, although some controversy exists in this nomenclature.

Atrial Tachycardias (Fig. 6–40; see also Figs. 18–4, 18–9, 19–3)

Atrial tachycardia is usually rapid and regular, originating from an ectopic supraventricular focus. Three or more consecutive APCs constitute atrial tachycardia, which is usually associated with organic heart disease. Its P′ waves are different in morphology from sinus P waves. Unlike sinus tachycardia, atrial tachycardia may be terminated by vagal maneuvers. The same factors that cause APCs are associated with atrial tachycardia. Other predisposing conditions include ventricular pre-excitation, disseminated intravascular coagulation, and blunt cardiac trauma. Atrial tachycardia with AV block is often due to digitalis toxicity.

ECG Characteristics

1. Rapid heart rate, greater than 160 beats/minute (> 180 in toy breed dogs); greater than 240/minute in the cat. Rhythm is regular in most cases but may be slightly irregular. Atrial tachycardia can be either intermittent (paroxysmal) or continuous. P′ waves are usually positive in lead II, with regular P′-P′ intervals.
2. P′ waves may not be easily recognized. They may be obscured by the fast ventricular rate or a prolonged P′-R′ interval.
3. P′ wave configuration is generally different from that of sinus P waves. If the atrial rhythm is irregular and the P′ waves are of varying configuration, the term "multifocal atrial tachycardia" is used.
4. QRS configuration is usually normal; alternatively, it is wide and bizarre due to bundle branch block, aberrant ventricular conduction, or ventricular pre-excitation.
5. The P′-R interval of the P-QRS is usually constant (1:1 AV conduction). At extremely high rates, vary-

ing degrees of AV block can occur (e.g., 2:1, 3:1, 4:1).

Arrhythmias Originating in the Atrioventricular Junction

ATRIOVENTRICULAR JUNCTIONAL PREMATURE COMPLEXES. (Fig. 6–41; see also Figs. 6–46, 18–6, 18–14). Atrioventricular junctional premature complexes are caused by the early firing of an ectopic AV junctional focus. The impulse spreads backward (retrograde) to the atria as well as forward (anterograde) to the ventricles. The term "junctional" is more accurate for describing rhythms that arise in the region extending from the atrial fibers approaching the AV junction to the bifurcation of the bundle of His. Junctional premature complexes are often associated with digitalis toxicity and similar causes described for APCs.

ECG Characteristics

1. The heart rate is usually normal. The rhythm is irregular due to the premature P′ waves that disrupt normal sinus-initiated P-wave rhythm.
2. The P′ wave is usually negative in lead II.
3. The premature QRS complex is usually normal in configuration but can be wide and bizarre due to bundle branch block, aberrant ventricular conduction, or ventricular pre-excitation.
4. The P′ wave may precede, be superimposed on, or follow the QRS, depending on the location of the ectopic focus and on the conduction velocity above and below the AV junctional focus. For example, the negative P′ wave precedes the QRS when retrograde impulse conduction is faster than anterograde conduction.
5. A *noncompensatory pause* is usually present. It is characterized by an R-R interval enclosing the premature complex that is less than twice the normal R-R interval duration.

ATRIOVENTRICULAR JUNCTIONAL TACHYCARDIA. In AV junctional tachycardia, the ectopic focus in the AV junction acts as a primary pacemaker that discharges faster than the inherent AV junctional rate of 40 to 60 beats/minute (in the dog). The term "enhanced AV junctional rhythm" is used for rates greater than 60 but less than 100 in the dog. It is usually impossible to differentiate atrial tachycardia from an AV junctional tachycardia, since the inverted P waves are superimposed on the QRS-T complexes. The term "supraventricular tachycardia" can be used for both arrhythmias.

Associated conditions include those disorders associated with atrial arrhythmias. Digitalis toxicity is often associated with an AV junctional arrhythmia.

ECG Characteristics

1. Heart rate is greater than 60 beats/minute in the dog. The rhythm is usually regular. Junctional tachycardia can be either paroxysmal or continuous.
2. P′ waves are negative in lead II and may precede, be superimposed on, or follow the QRS complex.
3. QRS configuration is usually normal or can be wide and bizarre as a result of bundle branch block, aberrant ventricular conduction, or ventricular pre-excitation.
4. The P′-R interval is constant. The P′-R interval for a high AV junctional focus is normal or longer when there is conduction delay below the AV junctional focus. At high heart rates, varying degrees of AV block can occur.

ARRHYTHMIAS ORIGINATING IN THE VENTRICLE

Ventricular Premature Complexes

(Fig. 6–42; see also Figs. 6–45, 6–46, 19–7)

Ventricular premature complexes (VPCs) represent impulses that arise from an ectopic ventricular focus. These depolarizations spread from cell junction to cell

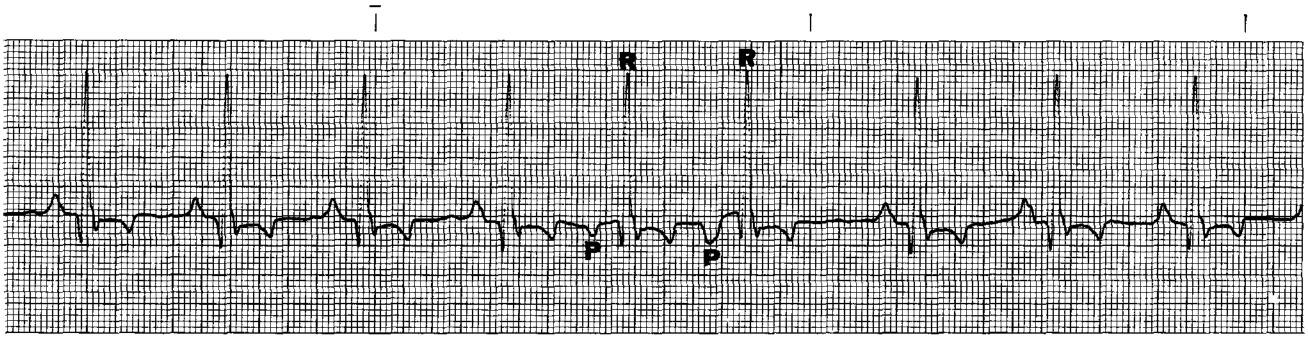


FIGURE 6–41

Two junctional premature complexes (fifth and sixth complexes) recorded from a dog with digitalis toxicity. P mitrale is also present.

FIGURE 6–42

Frequent ventricular premature complexes (VPCs) and paroxysmal ventricular tachycardia recorded from a dog with septicemia-endocarditis. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

junction rather than across the Purkinje system as would normally occur. This results in conduction delay with associated widening and bizarre contour of the QRS complex. Premature ventricular complexes comprise the second most common arrhythmia after sinus tachycardia. Two potential mechanisms include reentry and increased automaticity (chapter 16). Occasional VPCs by themselves do not cause hemodynamic impairment or clinical signs and should not be treated.

There are numerous causes of VPCs.[21, 30, 31, 57, 58] Occasionally, they may occur in normal hearts without clinical significance. Cardiac causes include heart failure due to congenital or acquired disorders; myocardial infarction; infection (especially viral or bacterial); inflammation; infiltrative myocardiopathies such as neoplasia; pericarditis; traumatic myocarditis; and idiopathic myocarditis, especially in boxers and Doberman pinschers. Inherited ventricular tachycardia is reported in German shepherds.[57] Secondary causes are numerous. Some of the more common include changes in autonomic tone; hypoxia; anemia; uremia; sepsis; disseminated intravascular coagulation and other coagulopathies; gastric dilation-volvulus; pancreatitis; nutritional deficiencies; and certain endocrinopathies (especially thyrotoxicosis). Cardioactive drug toxicities and certain anesthetics may be causative.

ECG Characteristics

1. Premature, ectopic QRS complexes are widened, bizarre, and often of large amplitude. The T wave is directed opposite to the QRS deflection.
2. Heart rate is usually normal. The rhythm is irregular due to the premature QRS complex that disrupts the normal sinus rhythm.
3. P waves are normal but are not associated with the premature, ectopic QRS-T complex. Independent normal P waves may precede, be within, or follow the VPC.
4. The ventricular origin of the VPCs can be suggested as follows: If the major QRS deflection is negative in lead II, the ectopic focus is in the left ventricle; the reverse is true for right-sided VPCs.
5. A *compensatory pause* usually follows a VPC. The ectopic ventricular impulse generally cannot penetrate the atrium retrogradely through the AV junction (see Figure 6–45). Therefore, the SA node is not depolarized and reset as usually occurs with supraventricular premature depolarizations, and the sinus rhythm continues undisturbed after the VPC. The R-R interval of the sinus-initiated QRS complexes on either side of the VPC equals twice the normally conducted R-R interval.
6. VPCs of identical shape are called unifocal; when ectopic QRS complexes are variable, they are termed multiform or multifocal VPCs.

Ventricular Tachycardia

(Figs. 6–42, 6–43; see also Figs. 18–21 through 18–24, 19–8, 19–9)

Tachycardias that are depicted by wide QRS complexes (CANINE >0.65 sec; FELINE >0.4 sec) are usually associated with ventricular tachycardia. Differential diagnoses of *wide QRS tachycardia* include supraventricular tachycardia with (1) aberration, (2) preexisting or functional bundle branch block, or (3) conduction over an accessory pathway.

A continuous series of three or more successive VPCs is termed ventricular tachycardia. It may be intermittent (e.g., paroxysmal) or persistent and sustained. Ventricular tachycardia is generally considered a serious and life-threatening tachyrhythmia that may cause hemodynamic impairment (e.g., syncope, weakness, hypotension) or electrical instability (e.g., ventricular fibrillation). Similar conditions that cause VPCs also predispose to ventricular tachycardia.

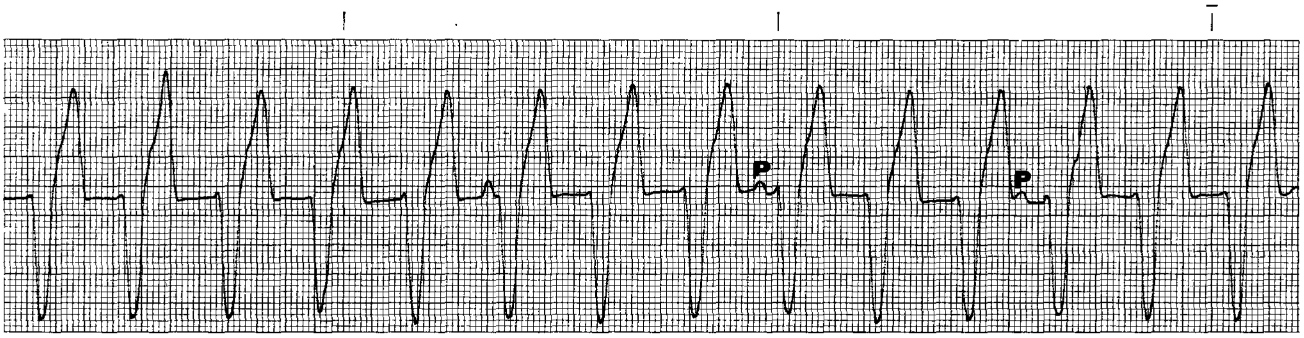


FIGURE 6–43

Sustained ventricular tachycardia from a dog with gastric torsion. There is no relationship between the QRS complexes and the P waves (called atrioventricular dissociation).

ECG Characteristics

1. Ectopic ventricular rate:
   CANINE—Greater than 100 beats/minute with a regular rhythm. Rates between 60 and 100 are termed *idioventricular tachycardia* or *enhanced ventricular rhythm.*
   FELINE—Usually greater than 150 beats/minute.
2. Ectopic QRS complexes are wide and bizarre, with T waves directed opposite the QRS deflection.
3. P waves, if visible, are normal in contour, but there is no association between them and the ventricular extrasystoles (termed "AV dissociation"). The independent normal P wave may precede, be within, or follow the VPC.
4. *Fusion complexes* imply ventricular activation from two different foci.
5. *Capture beats* by normal sinus-initiated rhythm or complexes may be present.

Ventricular Flutter and Fibrillation
(Fig. 6–44; see also Figs. 18–22 and 19–9)

These arrhythmias result in loss of consciousness and are usually fatal within minutes unless successful intervention is provided. Ventricular fibrillation is a terminal arrhythmia associated with cardiopulmonary arrest.[58] Ventricular contractions are weak and uncoordinated and do not eject blood (cardiac output ceases). The ECG shows irregular, chaotic, and deformed deflections of varying amplitude, width, and shape. Immediate defibrillation and cardiopulmonary resuscitation must be undertaken (chapter 21). Ventricular flutter presents as a sine wave in appearance, which is characterized by regular, large oscillations and may progress to ventricular fibrillation. They may not be easily distinguishable from rapid ventricular tachycardia.

ECG Characteristics

1. In ventricular fibrillation there are no discernible P-QRS-T complexes. Irregular, chaotic, low-voltage waves are present on the ECG.
2. There are two morphologic types of ventricular fibrillation: coarse (large oscillations) and fine amplitude. The latter is associated with worse survival rates.
3. Ventricular flutter displays regular, rapid, large sine wave-like oscillations.

Ventricular Asystole

Ventricular asystole denotes the absence of ventricular complexes and cardiac output. Associated with cardiopulmonary arrest, it carries a grave prognosis.[58] Ventricular asystole may be caused by severe SA block or sinus arrest, third-degree AV block, severe electrolyte or acid-base disorder, or other terminal systemic diseases.

ECG Characteristics

In cardiopulmonary arrest, there are no wave forms on the ECG—only a straight line. If associated with

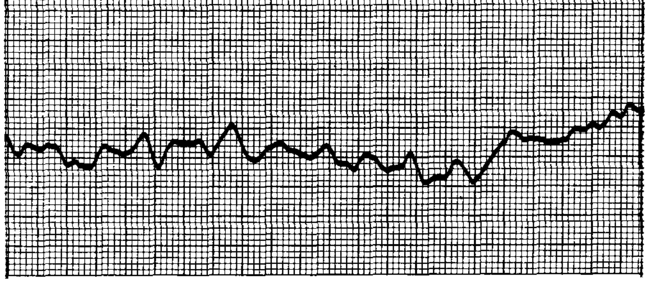


FIGURE 6–44

Coarse ventricular fibrillation. Disorganized oscillations without recognizable QRS-T deflections are evident. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

third-degree (complete) AV block, normal P waves occur but no QRS complexes are present. With severe SA block or arrest, the faster the original rate, the longer the period of asystole.

ADVANCED ELECTROCARDIOGRAPHIC CONCEPTS AND TECHNIQUES

LADDER DIAGRAMS (Figs. 6–45 and 6–46)

The ladder (Lewis) diagram is a graphic illustration of cardiac impulse formation and conduction. It is used to enhance understanding of arrhythmias and conduction disorders.[21, 59]

ABERRANT CONDUCTION

(Fig. 6–47; see also Figs. 18–3 and 19–4)

Aberration refers to abnormalities of a supraventricular impulse with abnormal or bizarre intraventricular conduction.[59–64] It occurs when a premature impulse conducts through cardiac tissue (bundle branches, Purkinje fibers, or myocardium) that is in its absolute or relative refractory period. This may be related to changes in cycle length, functional alterations in cellular electrophysiologic properties, electrolyte and metabolic abnormalities, or toxic drug effects. A form of aberrancy associated with effects of changing cycle lengths on refractoriness is known as the *Ashman phenomenon.* Duration of refractory period is related to the immediately preceding cycle length—the longer the preceding cycle, the longer the refractory period.

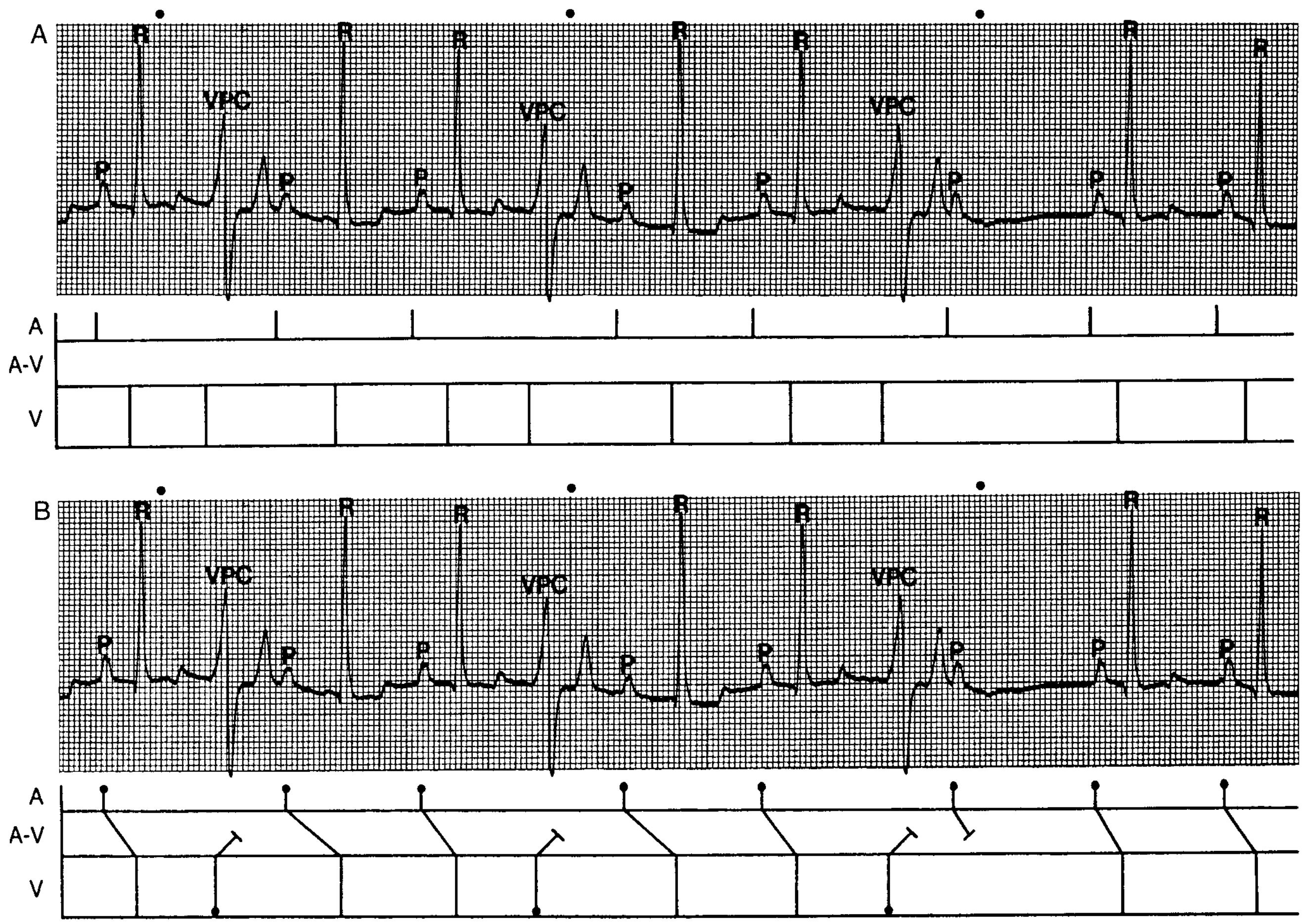


FIGURE 6–45

Technique describing use of the atrioventricular (AV) ladder diagram. (A) First, use a ruler to line up the beginning of the P waves with a subsequent vertical line drawn at the A (atrial) level. Then, line up the beginning of the QRS (Q wave) with the ventricular (V) level, and draw a corresponding vertical line. Finally, indicate AV conduction by connecting the bottom of the atrial line with the top of the ventricular line. A dot indicates the site of impulse formation. (B) The first two interpolated VPCs have penetrated the AV junction completely, rendering it temporarily refractory, and preventing ventricular conduction of the subsequent sinus-initiated P wave. A compensatory pause occurs after the third VPC. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

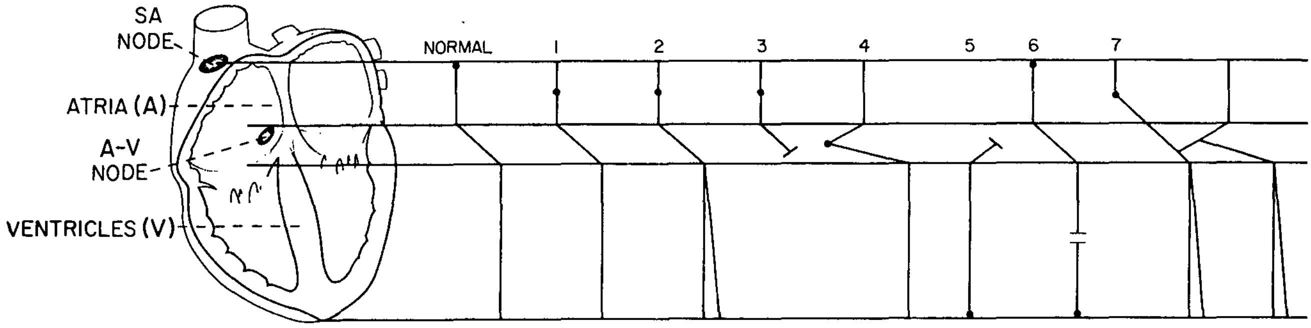


FIGURE 6–46

Representative examples of the atrioventricular (AV) ladder diagram: (1) Atrial premature complex (APC) with normal conduction; (2) APC with aberrant ventricular conduction (also used to illustrate left and right bundle branches); (3) nonconducted APC; (4) AV junctional premature complex with anterograde ventricular and retrograde atrial conduction; (5) ventricular premature complex (VPC) with partial penetration of the AV junction; (6) Fusion complex between a sinus impulse and an ectopic ventricular impulse; (7) APC and one reciprocal complex (re-entry) with aberrant ventricular conduction. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

Sudden prolongation of the immediately preceding cycle length with a relatively constant heart rate may cause aberration. The refractory period of the right bundle branch normally exceeds that of the left bundle branch. Therefore, aberration due to the Ashman phenomenon usually shows a RBBB configuration and must be differentiated from VPCs. If a P′ wave having a slightly prolonged P′-R interval precedes the aberrant QRS complex, intraventricular aberrant conduction of a supraventricular premature complex (versus a ventricular premature complex) is suggested (Fig. 6–47).

ECG Characteristics (Aberrancy Due to the Ashman Phenomenon)

1. Relatively long cycle immediately preceding the cycle terminated by the aberrant QRS complex.

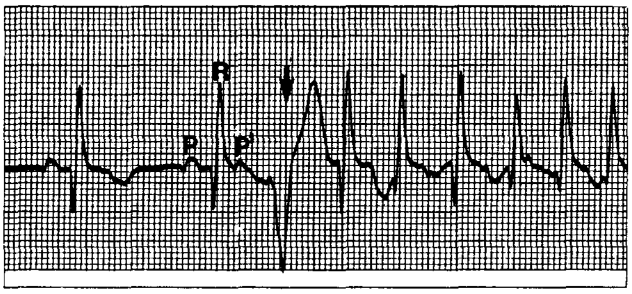


FIGURE 6–47

Aberrant ventricular conduction recorded from a dog. Atrial tachycardia is initiated by an APC (after the second sinus complex). This first APC contains a long P′-R interval with aberrant ventricular conduction (arrow). This aberrancy may represent the Ashman phenomenon, owing to the long cardiac cycle that preceded the short cycle. Secondary ST-T changes are also present. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

2. RBBB pattern of the aberrant QRS.
3. *Noncompensatory* pause following the aberrant QRS complex.
4. Irregular coupling of the aberrant QRS.

CONCEALED CONDUCTION

(Figs. 6–45 and 6–46)

Concealed conduction explains the phenomenon of incomplete cardiac impulse conduction through specialized conduction tissue (e.g., AV node) and emphasizes the importance of deductive reasoning in arrhythmia analysis. The effect of incompletely conducted impulses on subsequent electrocardiographic transcriptions is manifested by changes in the ensuing P-QRS-T complexes.[21, 64, 65] For example, retrograde impulse transmission of VPCs into the AV node may cause (1) conduction delay (i.e., prolonged conduction of normal supraventricular impulses down through the AV node, resulting in P-R interval prolongation [1° AV block]), (2) block of P wave transmission (e.g., 2° AV block); (3) displacement of the normal sinus pacemaker to another focus, (4) conduction enhancement, or (5) a combination of these. Although the presence of concealed conduction may often be deduced, further studies may be needed to confirm this possibility.

PARASYSTOLE

This term refers to arrhythmias characterized by (1) a varying coupling interval between the ectopic (parasystolic) complex and dominant, sinus complexes, (2) a common minimal time interval between interectopic intervals, with longer interectopic inter-

vals representing multiples of the minimal interval; the ectopic impulse is independent of, and "protected" from discharge by the dominant (sinus) rhythm, and (3) fusion complexes. This arrhythmia may originate in atrial AV junctional or ventricular tissues.[60–64]

RE-ENTRY (see Fig. 6–46)

Re-entry is a mechanism underlying many tachyarrhythmias (chapters 16 and 18). The electrical impulse that activates a cardiac tissue returns by a different pathway to reactivate the same tissue and thus, initiate reciprocating arrhythmias.[60–65] Purkinje fibers, ischemic myocardial tissue, bundle branches, His bundle, AV nodal tissue, and accessory AV pathways (WPW syndrome) all may function as a re-entrant circuit.

CONTINUOUS ECG (HOLTER) MONITORING (Fig. 6–48; see also Fig. 18–21)

The short, resting, lead II rhythm strip as generally performed during clinical examination has limited ability to intercept many arrhythmias. To enhance rhythm-sampling duration, continuous monitoring may be applied. This technique employs a precordial lead system (two or three electrodes positioned on the chest wall) connected to a portable, battery-powered ECG monitor. The ECG signal is recorded on magnetic tape or solid state unit, which is then analyzed by a special scanner (Fig. 6–48) or by using computerized techniques.

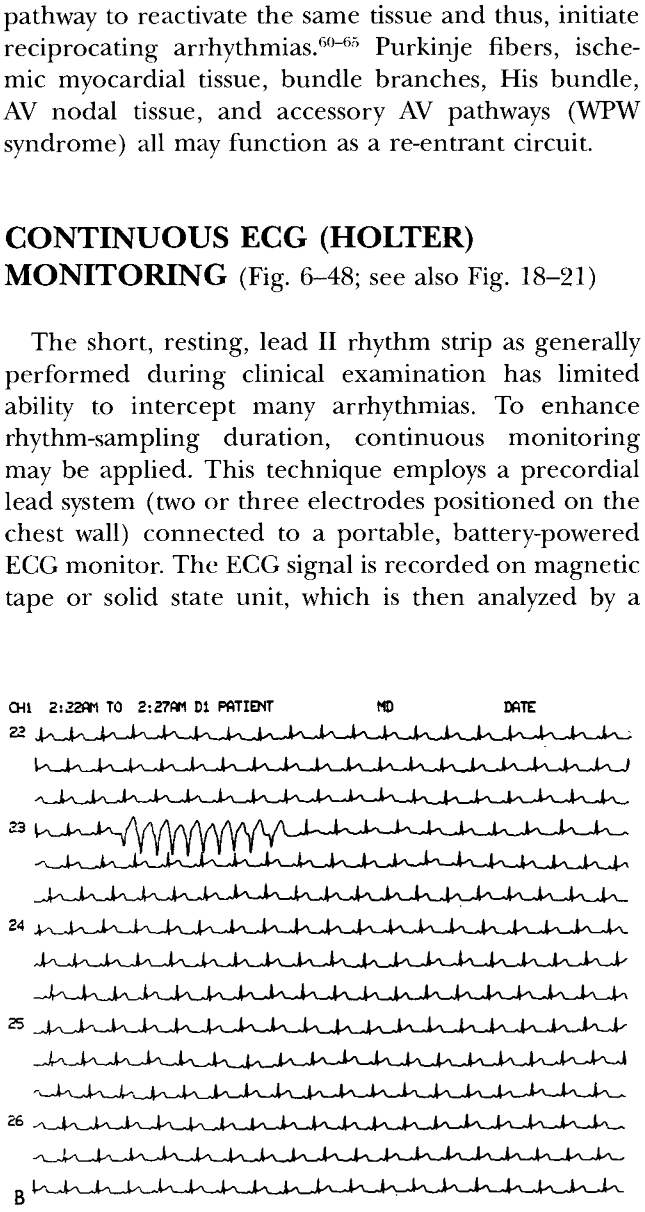


FIGURE 6–48

Printouts of a displayed time segment from a Holter monitor system. Paroxysmal ventricular tachycardia can be easily recognized and correlated with the time of occurrence by referring to digital time entries displayed adjacent to the ECG data. By this technique, arrhythmias can be recognized and graphically enlarged for complete analysis. (Courtesy of Del Mar Avionics, Irvine, California.)

Indications for long-term ECG monitoring include the need (1) to demonstrate suspected paroxysmal tachyarrhythmias, bradyarrhythmias, or conduction disorders when the routine ECG fails to record an arrhythmia, (2) to associate known rhythm disturbances with clinical signs such as syncope, (3) to document arrhythmias with hemodynamic significance, (4) to demonstrate arrhythmias with the potential for electrical instability, and (5) to assess efficacy of antiarrhythmic or pacemaker therapy (see chapter 18).[59, 60]

To highlight the relative lack of diagnostic accuracy provided by brief lead II rhythm strip recordings compared with 48-hour continuous monitoring, one study[66] compared the two techniques: the percentage of dogs with no ventricular arrhythmias recorded on ECGs performed every 6 hours, but with arrhythmia recorded by 48-hour continuous monitoring, was 25 percent when more than 3000 VPCs/hour were present; 50 percent with 1000 to 3000 VPCs/hour; and 100 percent with 10 to 300 VPCs/hour.

TRANSTELEPHONIC ELECTROCARDIOGRAPHY

Transtelephonic electrocardiography is well established in veterinary and human medicine and can accurately characterize rhythm disturbances and conduction abnormalities. It utilizes a small, portable, battery-powered, transistorized ECG preamplifier that converts ECG signals into tones that can be transmitted over the telephone line to a central receiving center staffed by specialists.[67]

In a clinical review of 2000 consecutive transtelephonic canine ECGs, 18 types of arrhythmias were detected in 20 percent (396) of the dogs. These included supraventricular arrhythmias (APCs, atrial tachycardia, atrial fibrillation, and atrial flutter); ventricular arrhythmias (VPCs, ventricular tachycardia and fibrillation); conduction disorders (1°, 2°, and 3° AV block, SA block and/or arrest, atrial standstill, and ventricular pre-excitation). Technical limitations of transtelephonic electrocardiography include attenuation of recorded voltages and inadequate frequency response of the mechanical system (recorder stylus), but these do not interfere with arrhythmia interpretation and diagnosis.

COMPUTED ELECTROCARDIOGRAPHY

Computed interpretation of the electrocardiogram has developed in human medicine; its contributions

include improved technical ECG quality; reduced need for medical record storage and improved routine surveillance for abnormalities; enhanced data retrieval; stimulated teaching; and reduced time needed for analysis and interpretation.[68] Manufacturers of electrocardiograph machines have added computed assessment of P-QRS-T wave forms to many of their newer models. The clinician should be wary of relying on these computed assessments, however, as they have been calibrated for human patients. In veterinary medicine, computed ECG analysis is still an emerging field.[59] In both human and veterinary application, it is mandatory that all ECGs be reviewed by an electrocardiographer so that computer analysis not be the final assessment. Currently available software programs cannot accurately interpret many complex arrhythmias, although they are effective in diagnosing common problems.

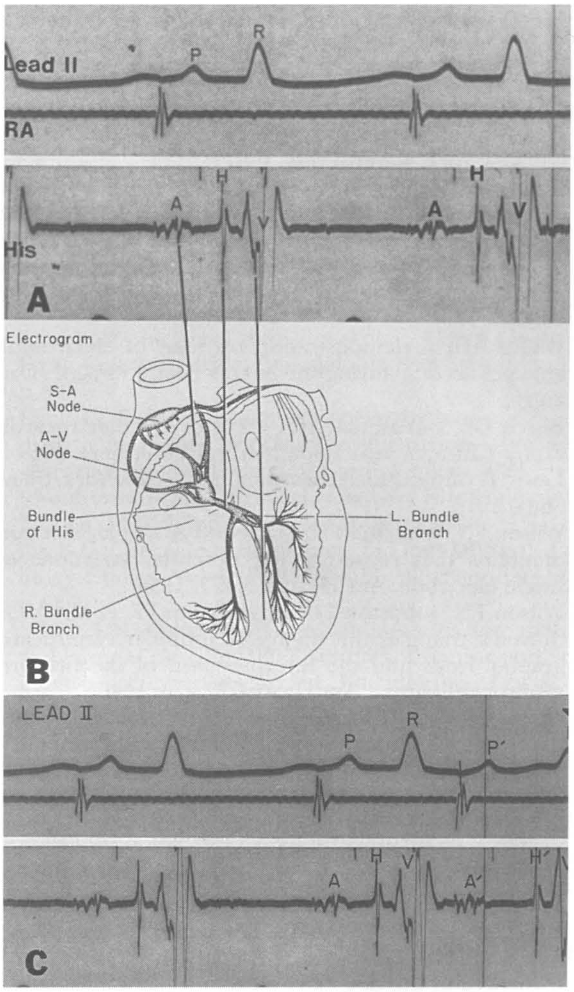


FIGURE 6–49

(A) Canine bundle of His *(His)* electrogram *(bottom)* recorded simultaneously with a right atrial *(RA)* electrogram *(middle)* and a lead II electrocardiogram *(top)*. (P, P wave; R, R wave; A, atrial deflection; H, His bundle deflection; V, ventricular deflection.) (B) His bundle electrogram (from [A] above) related to the corresponding conduction system sites illustrated by the in situ cardiac diagram. (C) Same scheme as in (A). The third complex from left *(arrow)* on the lead II ECG is of supraventricular origin. The P′ wave is premature; the His bundle electrogram displays a lengthened A′-H′ interval due to prolonged conduction through the AV node, which has not fully recovered from the previous impulse. The third complex (R′) represents aberrant conduction. (From Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, with permission.)

INTRACAVITARY ELECTROCARDIOGRAPHY (Fig. 6–49; see also Fig. 18–12)

A routine ECG does not provide detailed information about conduction system activation and may not indicate the presence of atrial activity (P waves). Intracavitary recordings can generate a cardiac electrogram using uni-, bi-, tri-, quadri-, or hexapolar catheters inserted in the right atrium or ventricle.[21, 59, 60] Special His bundle catheters can provide a His bundle ECG that records atrial and ventricular activity, atrium-to-His bundle conduction, His bundle-to-ventricle conduction, and other information. Atrial activity in complex tachyarrhythmias may be uncovered, aberrant ventricular conduction detected, site of AV block determined, conduction intervals between the atrium and His bundle and between the His bundle and ventricles defined, and arrhythmia ablation or cardiac pacing facilitated.

SIGNAL-AVERAGING ELECTROCARDIOGRAPHY

Signal-averaging electrocardiography (SAECG) is a technique for evaluating ventricular late potentials that occur during the terminal phase of the QRS complex or during the S-T segment. They represent low-amplitude (usually less than 1 μV) and high-frequency electrical activity.[69, 70] Specially placed surface electrodes are used to evaluate three bipolar ECG leads by a signal-averaging computer. The computer amplifies, filters, digitally samples, and then signal-averages the complexes to remove extraneous noise from the signal.

Ventricular late potentials occur in areas of injured myocardium that may serve as a site for re-entry and development of ventricular arrhythmias. Studies have shown SAECGs to identify some human patients who are at increased risk for developing sustained ventricular tachycardia and, to a lesser extent, sudden death. Experience in veterinary medicine is currently limited with SAECGs. Some boxers and Doberman pinschers with cardiomyopathy have been identified with ventricular late potentials on SAECGs. A few also had ventricular arrhythmias and experienced sudden death.[71]

REFERENCES

1. Opie LH. The Heart. Physiology and Metabolism. 2nd ed. New York, Raven Press, 1991
2. Kolliker A, Müller H. Nockweis der Negativen Schwankung des Muskelstrom am Naturlich sich contrahireiden Muskel. Verh Phys Med Ges 6:528, 1856
3. Lipman BS, Dunn M, Massie E. Clinical Electrocardiography. 7th ed. Chicago, Year Book Medical Publishers, 1984
4. Waller AD. A demonstration on man of electromotive changes accompanying the heart's beat. J Physiol (Lond) 8:229, 1887
5. Burch GE, DePasquale NP. A History of Electrocardiography. Chicago, Year Book Medical Publishers, 1964
6. Lewis T. Clinical Electrocardiography. New York, Shaw & Sons, 1913
7. Wilson FN, Johnston FD, Macleond AG, et al. Electrocardiograms that represent the potential variations of a single electrode. Am Heart J 9:477, 1934
8. Wilson FN, Johnston FD, Rosenbaum FF, et al. On Einthoven's triangle, the theory of unipolar electrocardiographic leads and the interpretation of the precordial electrocardiogram. Am Heart J 32:279, 1946
9. Norr J. Uber Hertzstromkurvenaufnahmen an Haustieren. Zur Einfuhrung der Elektrokardiographie in die Veterinärmedizin. Arch Wiss Prakt Tierhdikd 48:85, 1922
10. Detweiler DK. Electrocardiographic and clinical features of spontaneous auricular fibrillation and flutter (tachycardia) in dogs. Zentralbl Veterinaermed 4:509, 1957
11. Detweiler DK, Patterson DF. The prevalence and types of heart disease in dogs. Ann NY Acad Sci 127:481, 1965
12. Patterson DF, Detweiler DK, Hubben K, et al. Spontaneous abnormal cardiac arrhythmias and conduction disturbances in the dog (a clinical and pathologic study of 3,000 dogs). Am J Vet Res 22:355, 1961
13. Hamlin RL, Smith CR. Anatomical and physiological basis for interpretation of the electrocardiogram. Am J Vet Res 21:701, 1960
14. Hamlin RL, Smetzer DL, Smith CR. The electrocardiogram, phonocardiogram and derived ventricular activation process of domestic cats. Am J Vet Res 24:792, 1960
15. Hamlin RL. Electrocardiographic detection of ventricular enlargement in the dog. J Am Vet Med Assoc 153:1461, 1968
16. Hill JD. The electrocardiogram in dogs with standardized body and limb positions. J Electrocardiol 1:175, 1968
17. Moore EN, Morse HT, Price AC. Cardiac arrhythmias produced by catecholamines in anesthetized dogs. Circ Res 15:77, 1964
18. Moore EN, Jomain SL, Stuckey JH, et al. Studies on ectopic atrial rhythms in dogs. Am J Cardiol 19:676, 1967
19. Ettinger SJ, Suter PF. Canine Cardiology. Philadelphia, WB Saunders, 1970
20. Fox PR. Animal models of naturally occurring arrhythmias. *In* Dangman KH, Mura DS (eds): Electrophysiology and Pharmacology of the Heart. New York, Marcel Dekker, Inc, 1991, p 413
21. Tilley LP. Essentials of Canine and Feline Electrocardiography. Interpretation and Management. 3rd ed. Philadelphia, Lea & Febiger, 1992
22. Miller MS, Tilley L, Detweiler DK. Cardiac Electrophysiology. *In* Swenson MJ, Reece WD. Duke's Physiology of Domestic Animals. 11th ed. New York, Cornell University Press, 1993, p 105
23. Lazzara R. Basic electrophysiology. *In* Helfant R (ed): Bellet's Essentials of Cardiac Arrhythmias. Philadelphia, WB Saunders, 1979
24. Silver EN, Katz LN. Electrocardiography and vectorcardiography. *In* Heart Disease. New York, Macmillan, 1975, p 294

24a. Fisch C. Electrocardiography. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, 5th ed. Philadelphia, WB Saunders, 1996, p 108

25. Greenspan K. Cardiac excitation, conduction and the electrocardiogram. *In* Selkurt EE (ed): Physiology. 4th ed. Boston, Little, Brown, 1976, p 311
26. Horan LG, Flowers NC. Electrocardiography and vectorcardiography. *In* Braunwald E (ed): Heart Disease. Philadelphia, WB Saunders, 1980, p 198
27. Castellanos A, Myerburg R. The resting electrocardiogram. *In* Hurst JW (ed): The Heart. 6th ed. New York, McGraw-Hill, 1986, p 206
28. Abildskov JA. The electrocardiogram. *In* Sodeman WA (ed): Pathologic Physiology; Mechanisms of Disease. 5th ed. Philadelphia, WB Saunders, 1974, p 312
29. Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988

29a. Edwards NJ. Bolton's Handbook of Canine and Feline Electrocardiography. 2nd ed. Philadelphia, WB Saunders, 1987

30. Zipes DP. Specific arrhythmias: Diagnosis and treatment. *In* Braunwald E (ed): Heart Disease, 5th ed. Philadelphia, WB Saunders, 1996, p 705
31. Wynne J, Braunwald E. The cardiomyopathies and myocarditides: Toxic, chemical, and physical damage to the heart. *In* Braunwald E (ed): Heart Disease, 5th ed. Philadelphia, WB Saunders 1996, p 1404
32. Fox PR, Nichols CER. Cardiac involvement in systemic disease. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 565
33. Stang JM, Ryan JM. The magic of the electrocardiogram; Diagnostic utility of the scalar and vector ECG in the 1980s: A perspective. *In* Warren JV, Lewis RP (eds): Diagnostic Procedures in Cardiology: A Clinician's Guide. Chicago, Year Book Medical Publishers, 1985, p 51

33a. Schrope DP, Fox PR, Hahn AW, et al. Effects of electrocardiograph frequency filters on P-QRS-T amplitudes of the feline electrocardiogram. Am J Vet Res 56:1534, 1995

34. James TN, Robertson BT, Waldo AL, et al. De subitaneis mortibus, XV. Hereditary stenosis of the His bundle in Pug dogs. Circulation 52:1152, 1975
35. James TN. Congenital deafness and cardiac arrhythmias. Am J Cardiol 19:627, 1967
36. Stevenson WG, Perloff JK, Weiss JN, et al. Facioscapulohumeral muscular dystrophy: Evidence for selective, genetic electrophysiologic cardiac involvement. J Am Coll Cardiol 15:292, 1990
37. Jeraj K, et al. Atrial standstill, myocarditis and destruction of cardiac conduction system: Clinicopathologic correlation in a dog. Am Heart J 99:185, 1980
38. Holland CT, Cranfield PJ, Watson AD, et al. Dyserythropoiesis, polymyopathy, and cardiac disease in three related English Springer Spaniels. J Vet Intern Med 5:151, 1991
39. Patterson DF. Congenital defects of the cardiovascular system of dogs: Studies in comparative cardiology. Adv Vet Sci Comp Med 20:1, 1976
40. Spodick DH. Fascicular blocks: Not interpretable from the electrocardiogram. Am J Cardiol 70:809, 1992
41. Leitch J, Klein GJ, Yee R, et al. New concepts on nodoventricular accessory pathways. J Cardiovasc Electrophysiol 1:220, 1990

42. Wellens HJJ, Brugada PC, Penn OC, et al. Pre-excitation syndromes. *In* Zipes DP, Jalife J (eds): Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1990, p 691
43. Moore EN, Spear JF, Boineau JP. Arrhythmias and conduction disturbances in simulated Wolff-Parkinson-White syndrome in the dog. Am J Cardiol 6:650, 1971
44. Hill BL, Tilley LP. Ventricular preexcitation in seven dogs and nine cats. J Vet Med Assoc 187:1026, 1985
45. Rothfeld EL. The itinerant ST-T segment. Heart Lung 6:857, 1977
46. Detweiler DK. The dog electrocardiogram: A critical review. *In* MacFarlane PW, Lawrie TDV (eds): Comprehensive Electrocardiography: Theory and Practice in Health and Disease. New York, Pergamon Press, 1988
47. Oguchi Y, Hamlin RL. Rate of change of QT interval in response to a sudden change in the heart rate in dogs. Am J Vet Res 55:1618, 1994
48. Friedman HH. Diagnostic Electrocardiography and Vectorcardiography. 3rd ed. New York, McGraw-Hill, 1985
49. Liu SK, Fox PR. Myocardial infarction and ischemia. *In* Kirk RW, Bonagura JB (eds): Kirk's Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1992, p 791
50. Bonagura JD. Electrical alternans associated with pericardial effusion in the dog. J Am Vet Med Assoc 178:574, 1981
51. Fox PR, Broussard JD, Peterson ME. Electrocardiographic and radiographic changes in cats with hyperthyroidism: Comparison of populations evaluated during 1979–1993; Abstract. J Vet Intern Med 7:118, 1993

51a. Broussard JD, Peterson ME, Fox PR. Changes in clinical and laboratory findings in cats with hyperthyroidism from 1983 to 1993. J Am Vet Med Assoc 206:302–305, 1995

52. Jordan JL, Yamaguchi I, Mandel WJ. Studies on the mechanisms of sinus node dysfunction in the sick sinus syndrome. Circulation 57:217, 1978
53. Hamlin RL Smetzer DL, Breznock EM. Sinoatrial syncope in miniature Schnauzers. J Am Vet Med Assoc 161:1023, 1972
54. Bonagura JD, Ware WA. Atrial fibrillation in the dog and cat. Clinical findings in 81 cases. J Am Anim Hosp Assoc. 22:111, 1986
55. Harpster NK. The cardiovascular system. *In* Holzworth J (ed): Diseases of the Cat. Medicine and Surgery. Philadelphia, WB Saunders, Philadelphia, 1987, p 820.
56. Fox PR. Feline myocardial diseases. 18th Annual Waltham/OSU Symposium; Cardiology. Vernon, California, 1994, p 119
57. Moise NS, Meyers-Wallen V, Flahive WJ, et al. Inherited ventricular arrhythmias and sudden death in German shepherd dogs. J Am Coll Cardiol 24:233, 1994
58. Rush JE, Wingfield WE. Recognition and frequency of dysrhythmias during cardiopulmonary arrest. J Am Vet Med Assoc 200:1932, 1992
59. Tilley LP. Advanced electrocardiographic techniques. Vet Clin North Am 13:365, 1983
60. Chung EK. Principles of Cardiac Arrhythmias. 3rd ed. Baltimore, Williams & Wilkins, 1983
61. Zipes DP, Jacifes J (eds). Cardiac Electrophysiology; From Cell to Bedside. Philadelphia, WB Saunders, 1990, p 807
62. Fisch C. Electrocardiography of arrhythmias: From deductive analysis to laboratory confirmation—Twenty-five years of progress. J Am Coll Cardiol 1:306, 1983
63. Josephonson ME. Clinical Cardiac Electrophysiology. 2nd ed. Philadelphia, Lea & Febiger, 1993
64. Fisch C. Concealed conduction. *In* Zipes DP (ed): Cardiology Clinics. Vol 1. Philadelphia, WB Saunders, 1983, p 63
65. Miller MS, Calvert CA. Special methods for analyzing arrhythmias. *In* Tilley LP: Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, p 289
66. Marino DJ, Matthiesen DT, Fox PR, et al. Ventricular arrhythmias in dogs undergoing splenectomy: A prospective study. Vet Surg 23:101, 1994
67. Tilley LP. Transtelephonic analysis of cardiac arrhythmias in the dog. Vet Clin North Am 13:63, 1983
68. Sridharan MR, Flowers NC. Computerized electrocardiographic analysis. Mod Concepts Cardiovasc Dis 53(7):37, 1984
69. Simson MB. Use of signals in the terminal QRS complex to identify patients with ventricular tachycardia after myocardial infarction. Circulation 64:235, 1981
70. Calvert CA. High-resolution electrocardiography (signal-averaged electrocardiography) in normal Doberman pinschers and Doberman pinschers with occult cardiomyopathy. ACVIM Scientific Proceedings. New Orleans, 1991, p 693
71. Breithardt G, Borggrefe M. Recent advances in the identification of patients at risk of ventricular tachyarrhythmias: Role of ventricular late potentials. Circulation 75:1091, 1987

7

Radiology

PETER F. LORD

PETER F. SUTER

ROLE OF RADIOLOGY IN DIAGNOSIS AND MANAGEMENT OF THORACIC DISEASE

Thoracic radiography forms the cornerstone for evaluation of cardiopulmonary disease.[1, 2] Its value is to (1) provide direct information about cardiovascular size and shape; (2) indicate lesions or abnormalities in lung parenchyma, airways, and pleural and mediastinal spaces; (3) indirectly assess cardiopulmonary circulation; (4) reflect the degree of heart failure; and (5) disclose and help assess noncardiac conditions. A careful and systematic thoracic radiographic examination may facilitate, confirm, or exclude a particular clinical diagnosis suspected from the history and physical examination. It also aids in assessing the severity and significance of known heart disease and helps evaluate therapeutic efficacy.

Although many cardiorespiratory disorders manifest with similar clinical signs (e.g., coughing, dyspnea, fainting, or cyanosis), heart failure often can be differentiated from respiratory disorders on the basis of radiographic features. This is especially true when the history, clinical signs, and physical examination are not specific enough to confer a definitive diagnosis. Radiologic information may also illustrate the need for other diagnostic tests that would not otherwise be considered.

Echocardiography cannot replace radiography for evaluation of the coughing or dyspneic patient. The echocardiogram often provides useful information about cardiac anatomy and function. However, only radiography will indicate certain hemodynamic consequences of heart failure (e.g., pulmonary congestion), provide information about the respiratory system, help identify and differentiate clinical abnormalities attributable to many systemic, noncardiac diseases, and assist in assessing therapeutic response. Contrast studies such as angiocardiography (chapters 9, 24) and pericardiography (chapter 29) have declined in importance with the growing refinement of echocardiography. However, these techniques still maintain a place for definitive diagnosis of certain conditions. Thus, knowledge of cardiac anatomy is essential (Fig. 7–1).

RADIOGRAPHIC QUALITY

The natural contrast provided by air in the lungs outlines the heart, mediastinum, thoracic wall, diaphragm, and pulmonary structures. The opacity of the ribs, spine, and muscle mass is minimized, while the lungs and airways are optimally exposed.

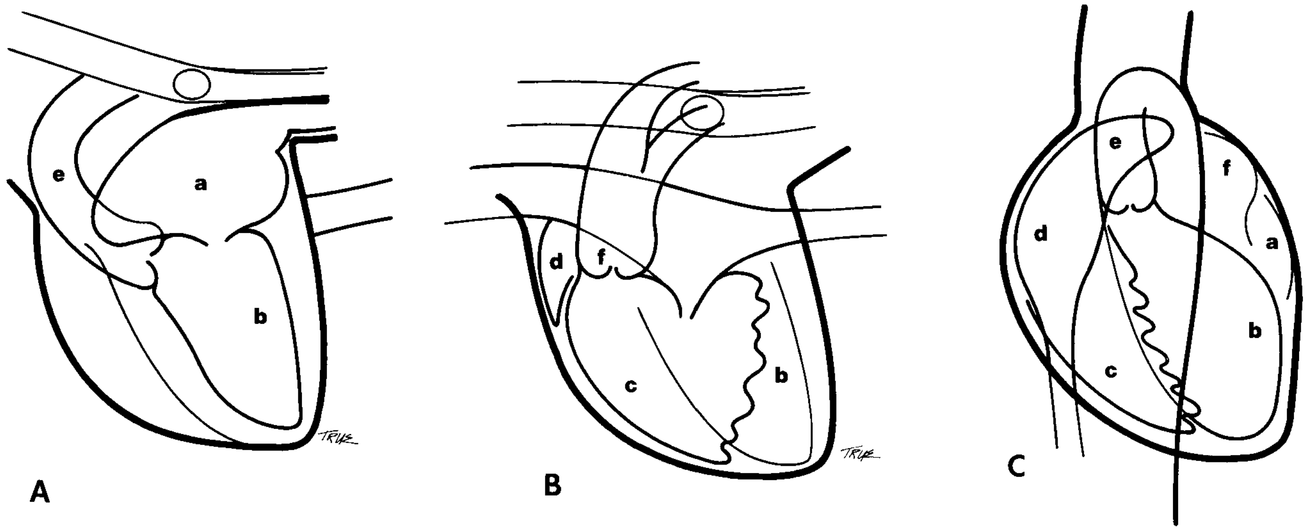


FIGURE 7-1

Schematic diagrams of the normal canine cardiac silhouette illustrating radiographic anatomy. (A, B) Right lateral view; (C) dorsoventral view. a, left atrium; b, left ventricle; c, right ventricle; d, right atrium; e, ascending aorta; f, pulmonary trunk.

TECHNICAL FACTORS

The clinician must master the technical factors that produce high-quality thoracic images.[1, 2] Time and effort spent in perfecting appropriate technique improves diagnostic accuracy. Poor image quality leads to frustration or misdiagnosis.

A technique chart that uses high kilovoltage (kV) and low milliamp-seconds (mAs) is best for thoracic radiography because it (1) minimizes exposure time, (2) reduces motion unsharpness, and (3) produces a low-contrast, high-latitude image that is ideal for thoracic organ interpretation. The exposure must place the parenchyma in the middle of the grey scale. The high latitude technique will ensure that some contrast remains in the spine and mediastinum. To avoid under- or overexposure, technique corrections must accommodate variations in proportion of tissue to air associated with breeds (e.g., bulldog vs. Afghan hound); chest conformation (e.g., obese vs. emaciated); and known diseases (e.g., pleural effusion vs. pneumothorax).

Standard development (either by the time-temperature method using fresh developer and fixer or an automatic film processor) is another essential element for reproducible diagnostic films. Old developer and fixer mars image quality.

Tranquillization (chapter 38) should be used judiciously and at a low dose when necessary to achieve a diagnostic image. In an uncooperative animal, potential risks of sedation should be weighed against the loss of diagnostic information from a distorted image, motion unsharpness, and underinflated lungs. Sedation may cause less stress than is incurred by manual restraint of a struggling animal, except in some states of shock or other conditions in which cardiac output is severely reduced.

EXPOSURE TIMES

"Fogging" caused by scattered radiation is not a great problem because most of the thorax contains air. It is more important that short exposure times (maximum 0.02 s) be used to offset effects of motion. For this reason, a grid should not be used even on fairly large dogs, if it increases exposure time so much that a blurred image would result. Rare earth screens can be 400 percent faster than standard high-speed screens, with no decrease in resolution. Their use, combined with an accurate electronic timer, usually will ensure acceptable films from a low-power machine. Exposure must be sufficient in the ventrodorsal (VD) or dorsoventral (DV) view to differentiate mediastinal structures, including aortic arch, descending aorta, main pulmonary arteries, trachea, and main bronchi.

RADIOGRAPHIC POSITIONING

Animals must be positioned straight since even slight obliquity in either lateral, ventrodorsal, or dorsoventral views distorts the cardiac silhouette and the diaphragm[2-4] and displaces the anatomic relationships between bronchi and pulmonary vessels. This makes it difficult to distinguish normal from abnormal structures. Radiographic positioning should be standardized. Either the right or left lateral view, or the DV or VD view, should be used routinely so that slight

differences between views[5, 6] are not misinterpreted as abnormalities.

RESPIRATORY PHASE

Ideally, radiographs should be exposed at peak inspiration to optimize contrast and detail.[2, 7] In dogs, radiographic changes have been reported relative to phase of respiration.

LATERAL RADIOGRAPH EXPOSED AT FULL INSPIRATION (compared to full expiration). At full inspiration there is (1) increased size of lung lobes cranial to the cardiac silhouette, (2) slight elevation of the silhouette from the sternum, (3) increased ventral tracheal angulation over the heart, (4) a flatter diaphragm with greater separation of diaphragm from caudal cardiac border, (5) a wider lumbar-diaphragmatic angle (generally caudal to T-12), and (6) a thinner, more elongated and distinct caudal vena cava that is more parallel to the vertebral column.

VENTRODORSAL RADIOGRAPH EXPOSED AT FULL INSPIRATION (compared to full expiration). At full inspiration there is (1) a smaller cardiac silhouette (more apparent than real due to decreased cardiothoracic ratio), (2) increased thoracic width (especially caudal to the 6th rib), (3) increased thoracic cavity length, (4) diaphragmatic dome positioned caudal to mid T-8, (5) a wider cardiodiaphragmatic angle with decreased cardiodiaphragmatic contact, and (6) a costodiaphragmatic angle located caudal to T-10.

DIFFERENCES BETWEEN RADIOGRAPHIC VIEWS

In lateral views, sternal contact is often greater in the left than the right lateral view, particularly in round-chested dogs (Fig. 7–2). The heart rotates slightly in the craniocaudal axis due to its weight, and it can move to a greater extent in a wide than in a thin thorax. Because increased sternal contact is a sign of right heart enlargement in the right lateral view, observation of normal contact as viewed in the left lateral view may be mistakenly interpreted as enlargement, especially if congenital heart disease or heartworms are suspected. Consistency with follow-up examinations is more important than which view is chosen initially,[5, 6] so that slight differences in shape are not mistaken for pathology.

Special conditions may affect the choice of DV or VD views. The animal may be uncomfortable or dyspneic, for example, and may not tolerate certain positions. It may be more difficult to pull the forelegs forward in the DV view. In addition, the hilar area and the pulmonary arteries in the caudal lobes are more sharply delineated in the DV view because the dorsal lung is better inflated with the animal in the prone position,[1, 6] making subtle signs of heartworm disease and peribronchial lesions more likely to be diagnosed. On the other hand, the projection of the lung field is larger in the VD view. In the cat, the lungs are normally better inflated in the VD views because the thorax is more expanded.[6] Mild pleural effusion may be missed in the VD view because the fluid gravitates to the paraspinal gutters formed by the rib curvature. Taking advantage of this fact, the suspicion of pleural

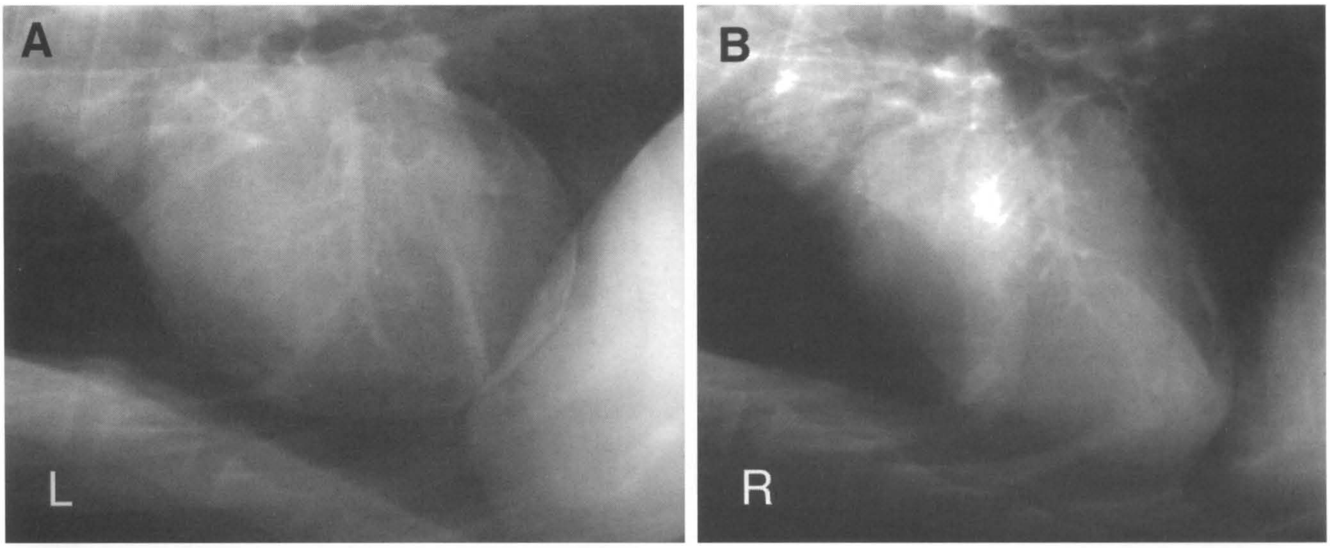


FIGURE 7–2

Left (A) and right (B) lateral views of a normal St. Bernard, a breed with a round thoracic conformation. Notice that sternal contact appears greater in the left compared with the right lateral view. These variations in cardiac shape and contact must not be misinterpreted as cardiac pathology.

effusion suggests use of a VD view if cardiac size and shape are to be evaluated, because fluid is less likely to obscure the cardiac silhouette in the VD than in the DV view.[2, 8]

LATERAL VIEWS

Obliquity makes the heart appear rounder. Instead of being superimposed on each other, the main stem bronchi are tilted, giving the impression of left atrial enlargement. When the thorax is straight in the lateral view, the dorsal arches of the ribs on each side will line up with each other.

DV AND VD VIEWS

The tips of the spinous processes should be within the bounds of the vertebral bodies.[3] The heart is more elongated in the VD than in the DV view. The technique must be set so that vessels are clearly visualized.

EXPOSURE TIMING

Ideally, the radiograph should be exposed at the peak of natural inspiration.[1, 2, 7] Poorly inflated lungs are a major source of misdiagnosis. Obese and panting dogs may not breathe deeply enough to provide good inspiration. Differences in inspiration and expiration were discussed earlier under Respiratory Phase.

EVALUATING CARDIAC SIZE AND SHAPE

Variations in conformation, positioning, and technique may create a false appearance of cardiac enlargement in animals suspected of having heart disease. Physiologic rather than pathologic conditions may affect heart size. The stage of respiration has been mentioned as an important factor.

CANINE BREED CONFORMATION

Normal variations in breed conformation can result in greater differences in relative heart size and shape than is caused by heart disease within a particular breed.[1, 2] It is essential to consider cardiac size and contour with reference to the particular conformation of the dog.

DEEP- AND NARROW-CHESTED DOGS. These have an elongated, more vertically oriented heart. In the DV view the heart may appear almost circular in shape.

ROUND-CHESTED DOGS. This other extreme in conformation may cause the heart to appear rounder and larger in the lateral view, with greater sternal contact. These hearts appear ovoid on the DV or VD views.

PUPPIES. Normally, puppies have relatively slightly larger hearts than do adult dogs. This can lead to an erroneous misdiagnosis of cardiomegaly in some cases.

OBESITY. Fat deposited around the heart can create the impression of cardiomegaly, particularly in the VD or DV view, which must be taken into consideration when evaluating the cardiac silhouette of obese animals.

FELINE BREED CONFORMATION

Cats have far less breed-related cardiac variation than dogs. Variation, when it occurs, is more individual rather than breed related.[9] The angle of cardiac long axis orientation is more variable than is the heart shape. Age-related changes in the feline cardiac silhouette have been reported. An exaggerated "horizontal" alignment of the heart (increased sternal contact) and tortuous, redundant aorta are a common variation in older cats.[10]

INFLUENCE OF THE CARDIAC CYCLE AND CIRCULATING BLOOD VOLUME

The stage of the cardiac cycle has a slight effect on size and shape.[11] External transverse diameter changes only 7 percent to make a volume change from diastole to systole of 50 percent in the normal ventricles.[12] This is because the linear dimensions are cubed to give volume measurements. Similarly, proportionately large increases in internal volume will cause a relatively small increase in external dimensions.

Changes in circulating blood volume have a major effect on cardiac size. Congestive heart failure increases blood volume and cardiac size. Dehydration (e.g., overdiuresis) may mask mild cardiac enlargement. Severe hypovolemia as may occur with hypoadrenocorticism or hemoperitoneum may reduce cardiac size.

METHODS OF CARDIAC EVALUATION

The heart may be evaluated by three methods: (1) the empiric method based upon memory (i.e., a men-

tal "library" of normal appearances and associated variations); (2) objective methods to evaluate cardiac enlargement, measuring dimensions, ratios, and areas.[13, 14] In the dog these efforts can be defeated by variations in conformation, positioning, and radiographic technique. However, a vertebral scale system to measure canine radiographic heart size has been reported, with good correlation between cardiac size and body length regardless of conformation;[14] and (3) a comparative method evaluating heart enlargement using previous films of the same animal, or films from an animal of the same breed. The last is generally the best method of evaluation.[15]

In contrast to the dog, the cat has little variation in conformation. Therefore, cats are more amenable to measurements of relative and absolute heart size.[9, 10, 16, 17]

LIMITATIONS OF RADIOGRAPHIC ASSESSMENT FOR CARDIAC ENLARGEMENT

The ability to evaluate chamber enlargement accurately by radiography is probably overrated.[18] A range of normal variations in cardiac size and shape overlaps pathologic enlargement and can be influenced by technical factors, positioning, and breed conformation.[1, 2] Thus, heart enlargement should be evaluated only within the context of other clinical findings.

Cardiac shape changes are usually easier to detect than are small changes in cardiac size. Noncardiogenic factors influencing cardiac shape include (1) breed conformation (especially dogs), (2) obesity, (3) stage of respiration and cardiac cycle, (4) dehydration or overhydration, (5) pleural effusion, and (6) poor radiographic positioning. Overdiagnosis of enlargement is common because of the desire to attribute clinical signs to congestive heart failure, especially when a heart murmur is present.[19] In contrast, with many cardiovascular disorders, whether or not clinical signs are present, the cardiac silhouette may appear radiographically within the normal range (Table 7–1). Therefore, lack of cardiomegaly does not always indicate absence of disease.

THE SMALL HEART

CLINICAL CAUSES. A small heart may result from decreased venous return. Etiologies include dehydration, overinflated lungs (physiologic, e.g., hyperpnea or upper airway obstruction; or pathologic, e.g., emphysema), shock, pneumothorax, and obstruction to venous inflow.[2]

TABLE 7–1
Conditions That May be Associated with a Relatively Normal Cardiac Silhouette

Small atrial and ventricular septal defects
Mild aortic and pulmonic stenosis
Functional murmurs
Bacterial endocarditis (early)
Focal myocarditis
Hypertrophic cardiomyopathy (mild)
Mild mitral or aortic regurgitation
Conduction disturbances
Constrictive pericarditis
Neoplasia
Congestive heart failure overtreated with diuretics (dehydration)

RADIOGRAPHIC APPEARANCE. In the lateral view, the long cardiac axis is shorter, making the trachea appear farther than normal away from the spine. The right-sided heart border and apex may be separated from the sternum, creating a gap that may be mistaken for pneumothorax, particularly on radiographs with too much contrast or that are overexposed. The apex is more pointed, and the transverse cardiac dimension is narrower. In the DV or VD view, the cardiothoracic ratio is decreased (Fig. 7–3).

GENERALIZED CARDIAC ENLARGEMENT

CLINICAL CAUSES. The cardiac silhouette generally enlarges in response to volume overload or myocardial failure or both. Volume overload may be caused by

FIGURE 7–3

Right thoracic radiograph of a 10-year-old, hypovolemic German shepherd in shock. Notice the small heart with the apex displaced away from the sternum; thin, spindly pulmonary vessels; and a very thin caudal vena cava. These changes are associated with severe hypovolemia.

valvular incompetence, central or peripheral arteriovenous shunts (e.g., patent ductus arteriosus, arteriovenous fistula, unrestrictive ventricular septal defects), or severe bradycardia (e.g., complete heart block). Myocardial failure may be primary (e.g., idiopathic dilated cardiomyopathy), or it may occur secondary to the chronic high wall stress of severe volume overload. Myocardial failure cannot be directly assessed by radiography. It may be determined by echocardiography noninvasively (chapter 8), cardiac catheterization and angiography (chapters 9, 24), or nuclear imaging or MRI (chapter 10).

The heart is enclosed in the pericardium, which under normal conditions tends to minimize focal protrusion of individual chambers. In most diseases, however, more than one chamber is affected by a volume or pressure load. For example, if the left ventricle fails from mitral regurgitation, the right ventricle may then fail secondarily, followed by right atrial and ventricular dilation. Neuroendocrine compensatory mechanisms cause fluid retention, which increases preload and contributes to volume overload and cardiac dilation. Thus, all chambers may be enlarged by certain lesions affecting the left ventricle.

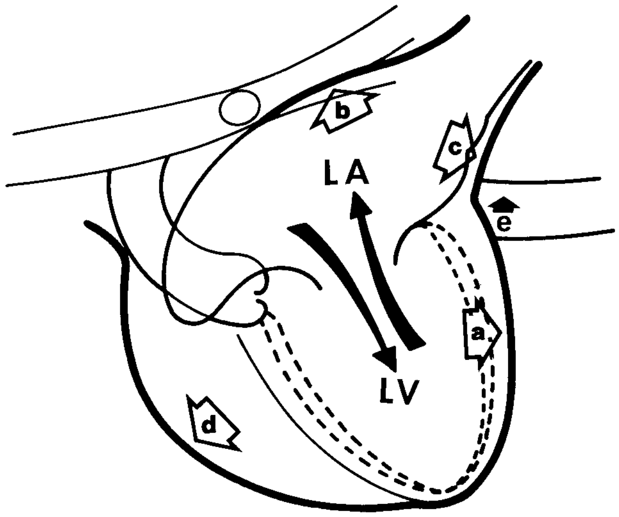


FIGURE 7–5

Schematic diagram showing cardiac changes associated with chronic volume overload due to mitral regurgitation *(long arrows)*. The inner broken line indicates the left ventricular chamber (LV) with associated resultant dilation (called *eccentric hypertrophy*). The outer broken line represents the left ventricle as would occur with secondary myocardial failure. Here, the LV is dilated with a thinner-than-normal LV wall. These differences in internal dimension and wall thickness are not detected on plain radiographs. Typical radiographic changes with chronic volume overload: the left ventricular border (a) becomes convex; the left atrium (LA) enlarges and displaces the left main stem bronchus (b); the LA bulges caudally (c); the right ventricular border becomes more convex (d) in response to an increased work load or myocardial failure; the caudal vena cava (e) is elevated *(small arrow)*.

RADIOGRAPHIC APPEARANCE. Cardiac enlargement is determined by the size of the heart compared with the thorax, and by displacement of adjacent structures. The heart appears wider in the craniocaudal, transverse, and long axes in both projections, and is generally rounder than normal (Figs. 7–4, 7–5, 7–6; see also Figs. 13–2, 13–3, 24–57*A*, 25–7, 27–4, 29–6, 29–16). The trachea is displaced dorsally, and the caudal vena cava may slope upward from the diaphragm to the heart.

In the VD/DV view, cardiothoracic ratios may be increased with generalized cardiomegaly (Fig. 7–6*B*; see also Figs. 25–7, 28–9*A*). The ratio of the maximal transverse width of the heart to the maximal transverse width of the thorax is greater than the normal 0.6 in the dog[13] and 0.67 in the cat.[16] These ratios are only a guide and are affected by variations in stage and depth of breathing and pleural and pulmonary diseases.

Several studies have evaluated methods to assess radiographic heart size. In dogs, heart measurements have not been regarded to be as sensitive as the trained eye.[15] However, a *vertebral scale system* has been reported

FIGURE 7–4

Schematic diagrams of the canine cardiac silhouette, showing enlargement of all chambers due to volume overload and/or myocardial failure. (A) Right lateral view; (B) dorsoventral view. The left ventricular border (a) is prominent; the left atrium (b) bulges dorsally, caudally, and laterally; the right ventricular border (c) is more convex and the right atrium (d) more prominent; the caudal vena cava is often widened.

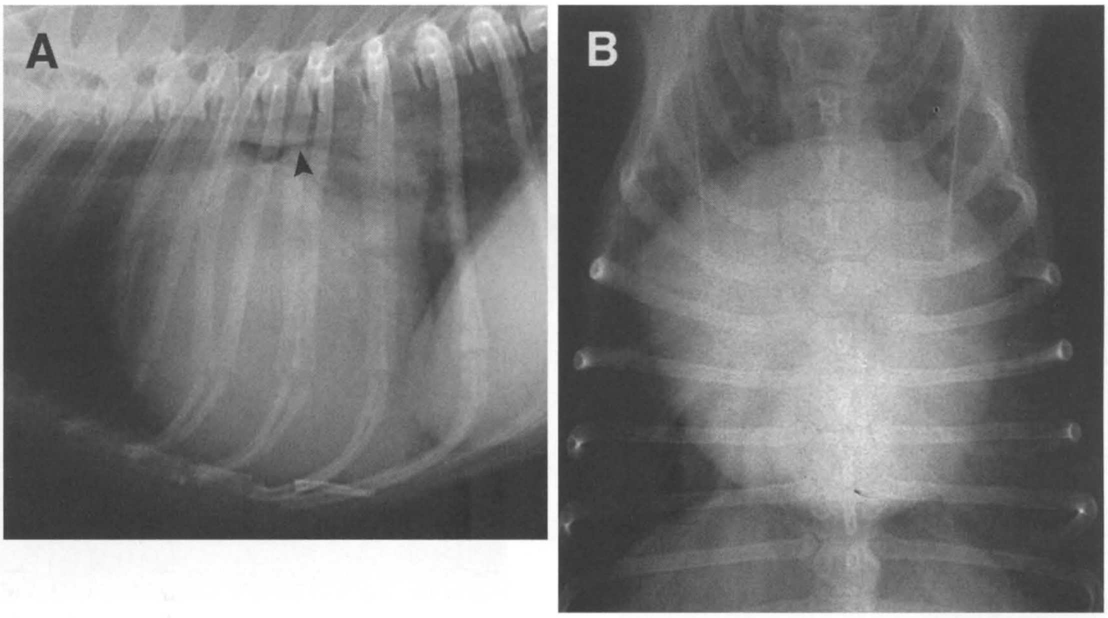


FIGURE 7–6

Generalized cardiac enlargement in a small-breed dog with chronic, severe, atrioventricular valve insufficiency (chronic myxomatous valvular degeneration, or endocardiosis). (A) Right lateral view showing diffuse interstitial edema in the dorsocaudal lung field and compression of the left mainstem bronchus *(arrow)*. (B) Ventrodorsal view showing generalized cardiomegaly.

to measure canine heart size in radiographs. It uses combined lengths of long and short cardiac axes scaled against the length of vertebrae above the heart, beginning with T-4. The sum of long and short axes calculated from 100 clinically normal dogs averaged 9.7 ± 0.5 vertebrae and was found to be generally reliable.[14] In cats, the ratio of the craniocaudal width of the heart to the distance between the cranial border of the fifth rib and the caudal border of the seventh rib may be a reliable indicator of cardiomegaly.[9]

In states of severe hyperpnea, the heart may not appear enlarged relative to the expanded thorax. A flat diaphragm and an open spinal-diaphragmatic angle are evidence of overinflation.

In the presence of pleural effusion, the heart is hidden, and the only indication of cardiomegaly may be the position of the trachea. In the cat, tracheal elevation in the presence of pleural effusion has been shown to be unreliable because the heart is displaced dorsally with moderate and severe fluid accumulation.[20] In the dog, when the trachea is dorsally displaced just cranial to the heart, a heart base mass should be suspected (see Fig. 29–16); when the trachea is elevated over the left atrium, left ventricular and left atrial enlargement is most frequently the cause (see Figs. 7–6, 25–7).[2, 18]

Severe right atrial and ventricular enlargement in congenital tricuspid valve dysplasia (Fig. 7–7; see also Fig. 24–57*B*) may resemble severe generalized cardiac enlargement or pericardial effusion. However, in the former, the apex of the heart is usually still apparent but may be obscured by the diaphragm; with moderate to severe pericardial effusion, all distinction of specific cardiac chambers is lost and replaced by generalized rounding of the cardiac silhouette (Figs. 7–13, 29–6 and 29–16).

LEFT VENTRICULAR ENLARGEMENT

CLINICAL CAUSES. In most cardiac disorders, left ventricular enlargement is accompanied by left atrial enlargement. Exceptions may include left ventricular pressure overload (e.g., aortic valve stenosis or systemic hypertension) and some cases of myocardial disease in which left ventricular wall thickening occurs with or without minimal left ventricular chamber dilation (Table 7–1). These conditions are best assessed by echocardiography. Isolated left ventricular enlargement is uncommon and difficult to detect by radiography.

RADIOGRAPHIC APPEARANCE. The entire caudal heart border changes in shape from the normal convex to a straight or bulging left heart wall formed by the enlarged left atrium and left ventricle (Fig. 7–4; see also Figs. 13–2, 24–17, 24–35, 24–57*A*, 24–59, 25–7, 27–5, and 34–4). Left atrial enlargement is a reliable radiographic indicator of left ventricular disease.[2]

LEFT ATRIAL ENLARGEMENT

CLINICAL CAUSES. The left atrium may enlarge in response to left-sided volume overload (e.g., chronic ac-

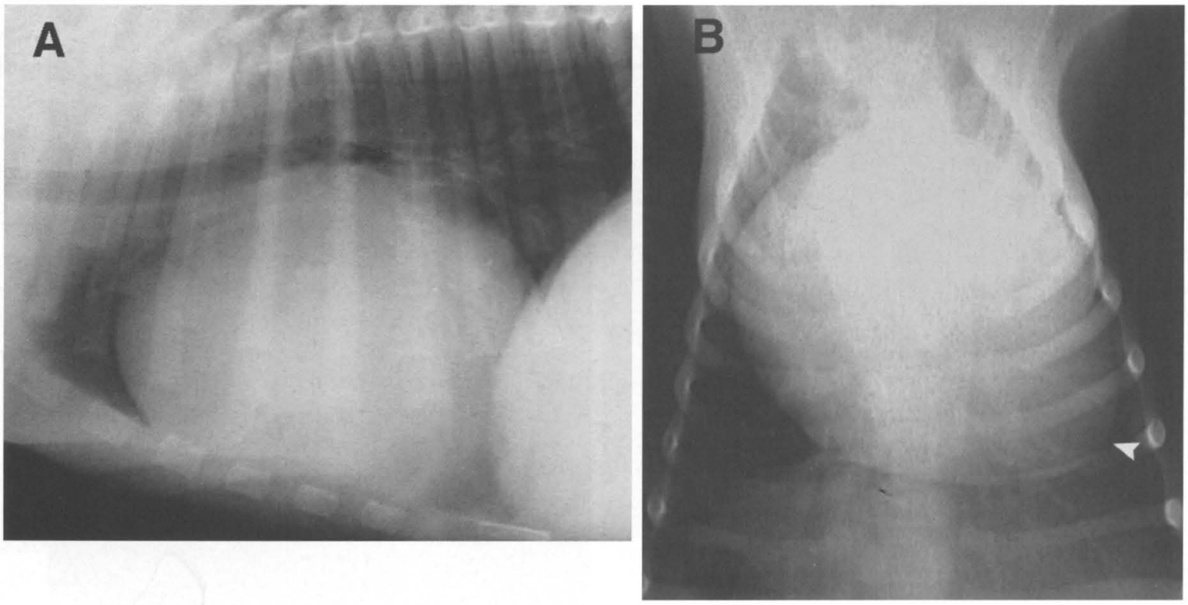


FIGURE 7–7

Severe right-sided heart enlargement in a three-month-old bull terrier with severe tricuspid valve dysplasia and insufficiency. (A) In the right lateral view the heart has a rounded appearance because the apex is elevated and obscured by the diaphragm. This could be confused with generalized cardiomegaly or pericardial effusion. (B) The ventrodorsal view reveals gross right-sided enlargement by the cardiac apex *(arrow)*, which is displaced toward the 4 o'clock position.

quired atrioventricular valve degeneration, mitral valve vegetative endocarditis, congenital left-to-right shunts such as patent ductus arteriosus), most cardiomyopathies, and mitral valve stenosis.[1, 2, 18, 21–23] High-output states such as feline hyperthyroidism and, occasionally, chronic, severe anemia will also cause left heart enlargement.[21]

RADIOGRAPHIC APPEARANCE. In the lateral view, the angle between the trachea and the caudal border of the left atrium (dorsal to the caudal vena cava) changes with progressive left atrial enlargement from obtuse, to a right angle, and then to an acute angle.[1, 2] The caudal border of the heart changes from a normal convex shape to a straight, then S-shaped or concave appearance (Figs. 7–4 to 7–9; see also Figs. 7–20; 13–2 to 13–4; 24–17, 24–57*A*, 24–59). A notch in the caudal heart border (*caudal waist*) may mark the atrioventricular groove (Figs. 7–8, 7–9; see also Figs. 7–20; 24–57*A*, 24–59), accentuated by severe left atrial enlargement. The entire caudal trachea, left main stem bronchus (especially in dogs), or both bronchi are displaced dorsally (Figs. 7–1, 7–5, 7–6*A*, 7–20; see also Figs. 24–17*B*, 24–35). Small dogs with severe, chronic mitral regurgitation may have an especially large left atrium that compresses the left main stem bronchus (Fig. 7–6*A*), especially with expiration or coughing. These dogs are also prone to tracheal collapse, especially when obesity is present. Lateral films may have to be taken at inspiration and expiration to confirm this bronchial collapse if fluoroscopy is not available. Mechanical bronchial impingement by the left atrium may induce coughing even in the absence of congestive heart failure.

In the VD/DV views, the left auricle may bulge beyond the left ventricular border at the 2 to 3 o'clock

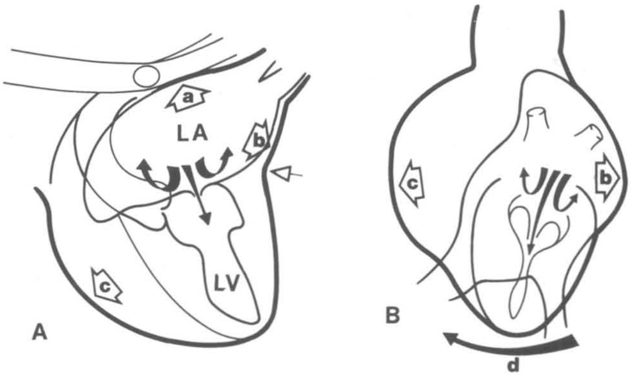


FIGURE 7–8

Schematic diagrams of feline hypertrophic cardiomyopathy. The thickened, stiff, noncompliant left ventricle (LV) increases diastolic resistance to ventricular filling *(curved arrows)*. Increased left atrial end-diastolic pressure results. This, when combined with mitral regurgitation (which usually accompanies changes in the mitral valve complex), causes left atrial enlargement. (A) In the right lateral view, the large left atrium (LA) displaces the trachea dorsally (a); the left atrium bulges caudally and laterally (b), creating a notch *(open arrow)* in the caudal heart border. (B) In the dorsoventral (DV or VD) view, the large left auricular appendage causes a prominent bulge (b) at 2 to 3 o'clock. The right ventricle usually enlarges secondarily to left-sided heart pathophysiology and/or tricuspid regurgitation (c). The cardiac apex may shift to the right (d) by the enlarged left atrium.

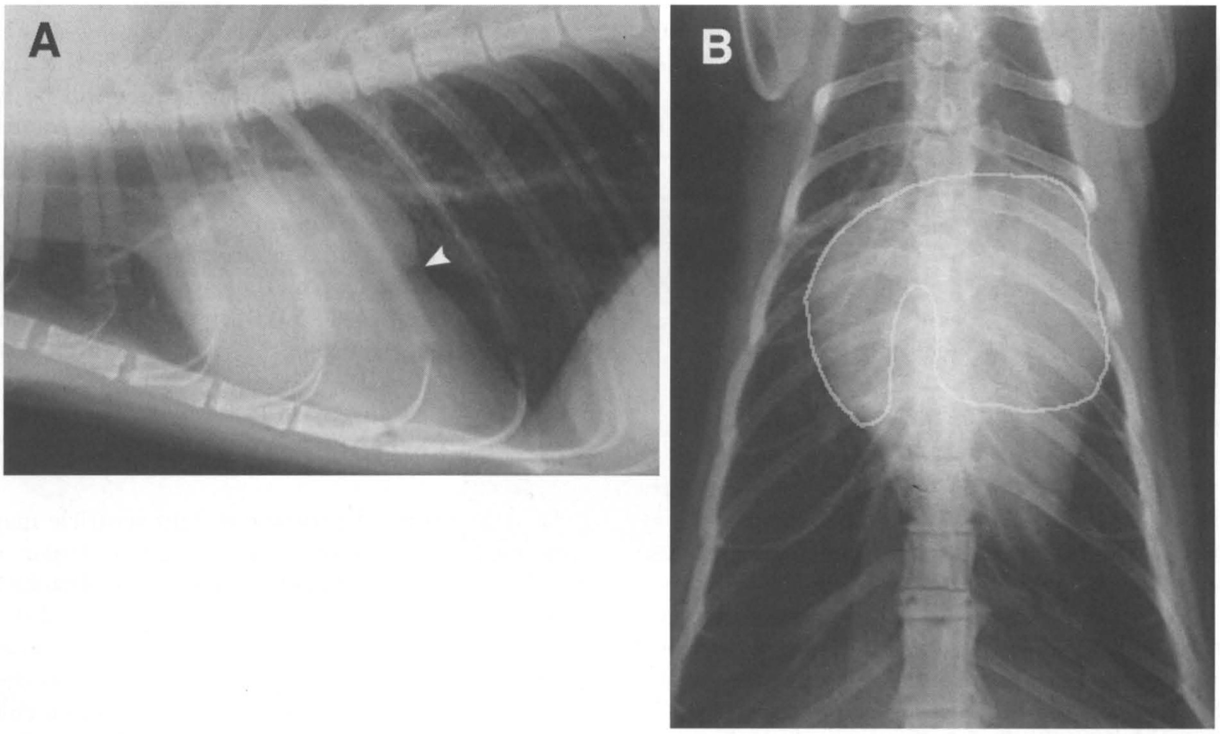


FIGURE 7–9

A cat with hypertrophic cardiomyopathy. (A) In the right lateral view the left side of the heart is elongated, causing the overlying trachea to become elevated toward the spine. The heart is wider than normal and has a notch *(arrow)* in the caudal heart border. This indicates left atrial enlargement dorsal to the notch. Note the dorsal displacement of the caudal vena cava at its junction near the heart. (B) On the ventrodorsal view, there is biatrial enlargement *(outlined)*, especially the left atrium.

position (Figs. 7–6*B*, 7–9*B*; see also Figs. 13–4*A*; 28–9*A*; 34–4*A*). With extreme left atrial enlargement, as in congenital or long-standing mitral regurgitation, mitral stenosis, or feline hypertrophic cardiomyopathy, the left atrium may be outlined as a distinct mass superimposed on the heart.[23, 24] It may be most notable in the DV/VD view situated between the main stem bronchi and is especially evident when employing relatively high kilovoltage (kV) to visualize the large airways in the mediastinum. In cats with severe hypertrophic or restrictive cardiomyopathy, the left atrium is disproportionately larger than the left ventricle. The caudal cardiac waist is accentuated, creating a bean-shaped heart in the lateral view (Fig. 7–8*A*) and a prominent left atrial appendage at 2 to 3 o'clock in the VD/DV view (Fig. 7–8*B*; see also Fig. 28–9). The VD/DV view is most sensitive for detecting left atrial enlargement in cardiomyopathic cats (chapter 28).

There is no consistent direct relationship between left atrial size and the degree of left ventricular failure. Often the left atrium is severely enlarged before congestive heart failure (CHF) develops (Figs. 7–9, 7–20).[23, 24] In chronic mitral regurgitation, the large compliant left atrium buffers the lungs from the regurgitated blood. End-diastolic (filling) pressure does not increase initially because the ventricle maintains its compliance as it enlarges (eccentric hypertrophy).[25] As the regurgitant volume increases and volume of forward cardiac output falls, diastolic ventricular blood volume increases, causing pressure in the pulmonary venous capacitance beds to increase (chapters 3, 11). Coupled with neuroendocrine system activation, this incites compensatory mechanisms of proximal venodilation, peripheral vasoconstriction, and increased lymphatic drainage to protect the lungs from pulmonary edema. The balance of these factors may be upset acutely, precipitating alveolar pulmonary edema (chapter 13). A contrasting situation exists in the case of acute aortic[26] or mitral regurgitation. The limits of myocardial and pericardial distention are reached with a small increase in volume because of inadequate time to adapt to the sudden load. Rapidly progressive dilated cardiomyopathy may develop pulmonary edema with only moderate cardiac enlargement.

In feline hypertrophic and restrictive cardiomyopathies, the stiff left ventricular wall reduces chamber compliance, impedes diastolic left atrial emptying during diastole, and increases left ventricular end-diastolic filling pressures (chapter 28). Progressive left atrial enlargement results, protecting the lungs from acute pulmonary edema. There is usually much less dramatic change in the external contour of the left ventricle.

The heart commonly rotates clockwise on the VD/DV view, so that the apex appears on the right side[16] (Fig. 7–8*B*).

RIGHT ATRIAL ENLARGEMENT

CLINICAL CAUSES. Most of the disorders causing right ventricular enlargement (discussed next) also result in right atrial enlargement.[27–33] The right atrium dilates in response to chronic volume and pressure overloads in a manner similar to that in the left atrium. In congenital tricuspid valve dysplasia with severe regurgitation, the right atrium may become huge before congestive heart failure ensues.[2, 33] Radiographic right atrial and ventricular enlargement in congenital tricuspid dysplasia may be difficult to differentiate from mild to moderate pericardial effusion (Figs. 7–7, 7–13; see also Fig. 24–57*B*). Identifying the apex of a severely enlarged heart and evaluating each side is the best way to differentiate the presence of right ventricular enlargement from generalized cardiomegaly (Figs. 7–10, 7–11, 7–12; see Fig. 7–7). A large, right atrial hemangiosarcoma may also cause the right atrium to bulge slightly. However, the surrounding pericardium and the presence of pericardial or pleural fluid render the radiographic examination insensitive for this disease.[34]

RADIOGRAPHIC APPEARANCE. On the lateral view, the cardiac silhouette may bulge cranially due to enlargement of the right atrial appendage (Figs. 7–4*A*, 7–7*A*; see also Fig. 31–2). The angle formed by the cranial vena cava and the cranial heart border will be filled in with loss of the *cranial waist*, and the transverse (craniocaudal) cardiac axis will be increased or enlarged. The trachea may be elevated as it passes over the cranial part of the heart.

In the DV or VD views, a large right atrium causes a bulge at 9 to 11 o'clock on the cardiac silhouette (Figs. 7–4*B*, 7–7*B*; see also Figs. 28–9; 30–7; 34–4*A*). This is caused by enlargement of the right atrial appendage.

RIGHT VENTRICULAR ENLARGEMENT

CLINICAL CAUSES. A prominent right ventricle may result from high resistance to right ventricular ejection.[27–32] Increased pulmonary vascular resistance may occur with chronic lung disease (cor pulmonale); pulmonary hypertension (heartworm disease, thromboembolism, or idiopathic); hypertensive patent ductus arteriosus or ventricular septal defect (Eisenmenger's syndrome); and by fixed ventricular outflow obstruction as in pulmonic stenosis and tetralogy of Fallot. Right ventricular volume overload or myocardial failure also causes right ventricular and atrial enlargement.[2, 32] Causes include congenital or acquired tricuspid or pulmonic valve insufficiency; dilated cardiomyopathy; severe left-sided heart disease (especially endocardiosis with severe mitral regurgitation); and, uncommonly, large ventricular septal defect with left

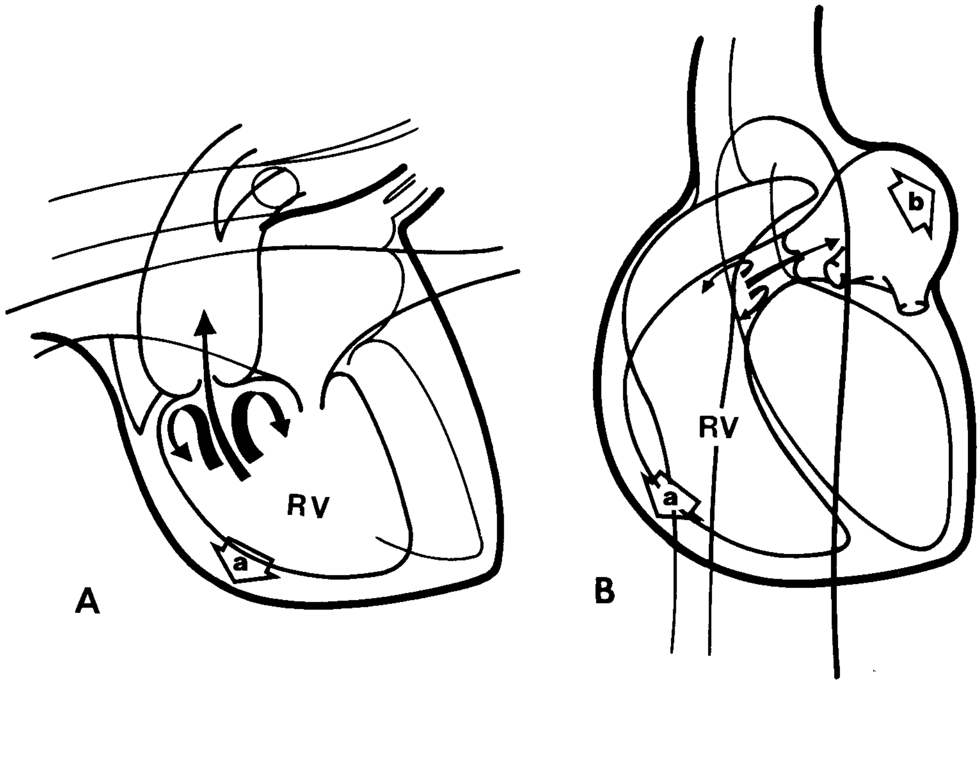


FIGURE 7–10

Schematic diagrams of right ventricular enlargement caused by a pressure overload (e.g., pulmonic stenosis). Because of the fixed outflow obstruction, right ventricular emptying is reduced *(curved arrows)*, and systolic pressure rises. Right ventricular wall hypertrophy occurs secondarily; the right ventricle becomes more rounded and the border more convex (a). (A) In the lateral view, sternal contact increases (a), which may push the apex dorsally off the sternum (apex tipping). (B) In the VD/DV view, the main pulmonary artery (pulmonary trunk) (b) bulges at the 2 o'clock position. The heart is rotated counterclockwise due to the large right ventricle (RV).

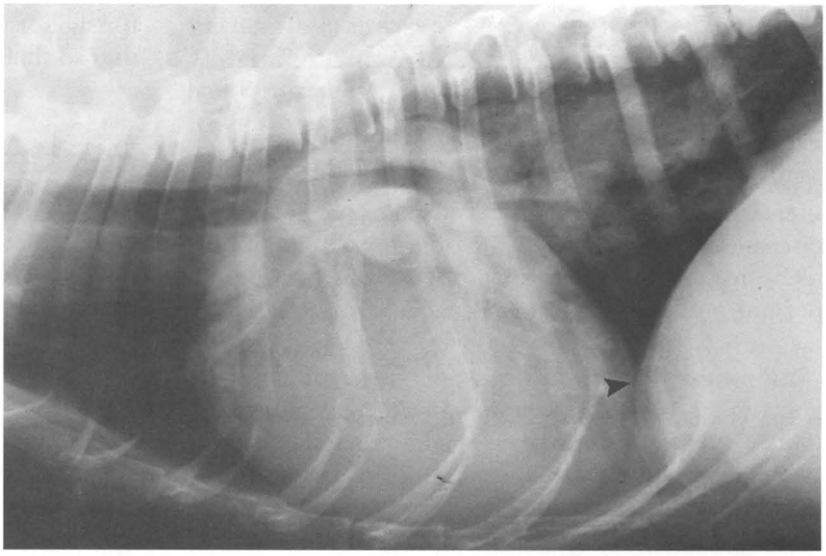


FIGURE 7–11

Right lateral view of heartworm-infected dog. The right ventricle is severely enlarged, indicated by increased heart width, increased sternal contact, and elevated cardiac apex *(arrow)*. Note that the caudal (left) heart border is relatively convex, indicating no left-sided enlargement. Radiographic evidence of heartworms includes (1) perihilar opacity of the dilated main pulmonary arteries, (2) severely widened and tortuous caudal arteries, and (3) widened cranial arteries.

ventricular to right atrial shunting, or anomalous pulmonary venous connections.

RADIOGRAPHIC APPEARANCE. The effect of these loads on the right ventricle is different from those imposed on the left side of the heart.[31, 32] The low pressure at which the right ventricle normally operates permits it to have a thin wall and a large radius of curvature. A volume overload (e.g., tricuspid regurgitation) or acute pressure overload (e.g., pulmonary thromboembolism) may cause the chamber to dilate. By contrast, a chronic pressure load from pulmonic stenosis, cor pulmonale, or left ventricular disease will cause concentric hypertrophy, which thickens the right ventricular wall and makes the chamber resemble the left ventricle (Fig. 7–10). Both pressure and volume overload will enlarge the right ventricular contour on the radiograph.[2]

On the lateral view, right ventricular enlargement is determined by accentuated heart convexity cranial to the apex. This causes the characteristic findings of (1) increased sternal contact (Figs. 7–4*A*, 7–6*A*, 7–7*A*, 7–10*A*, 7–11; see also Figs. 24–7, 24–57*B*; 30–8; 31–1, 31–2, 31–3*A*), and (2) "apex tipping" (i.e., the apex is pushed dorsally off the sternum if severe right ventricular enlargement is present without an enlarged left side of the heart) (Fig. 7–11; see also Fig. 31–3*A*). The trachea is usually elevated where it passes over the cranial heart. In the lateral view, right ventricular enlargement may be underestimated because the heart may rotate to the left as it enlarges.

On the VD/DV view, right ventricular enlargement creates a more convex border to the right of the apex (which is normally at the 5 to 6 o'clock position). The convexity extends clockwise to about the 10 o'clock position (Figs. 7–7*B*, 7–12; see also Figs. 24–28*A*; 30–8*B*). If there is no left-sided heart enlargement, the enlarged right ventricle will create a "reverse-D" contour (Figs. 7–10*B*, 7–12; Fig. 24–28*B*). Rather than bulging out toward the right thoracic wall, the heart often rotates counterclockwise to move the apex farther to the left (Fig. 7–12). An enlarged main pulmonary artery is often apparent (Fig. 7–12; see also Fig. 24–7, 24–10, 24–51; 30–8; 31–3), except in tetralogy of Fallot when the pulmonary trunk is hypoplastic.

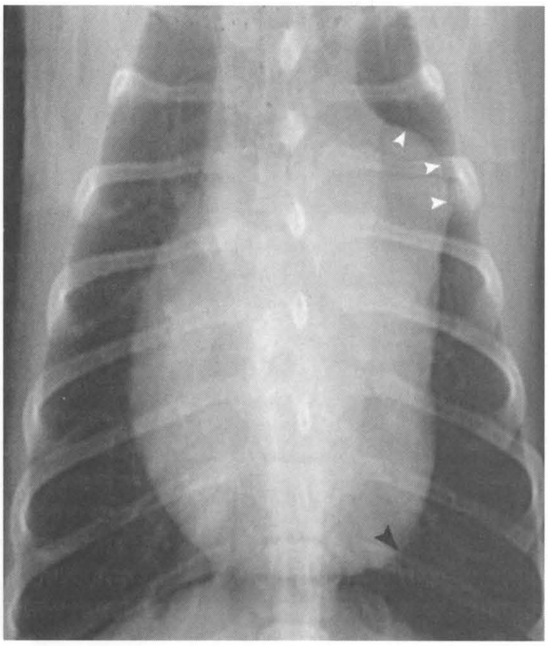


FIGURE 7–12

Ventrodorsal view of the heart of a Shih Tzu with congenital pulmonic stenosis. Right ventricular enlargement is indicated by the reverse "D" appearance. The cardiac apex *(black arrow)* separates the relatively straight left ventricle from the prominently convex right heart border.

PERICARDIAL DISEASES

PERICARDIAL EFFUSION

CLINICAL CAUSES. Etiologies and pathophysiology are discussed in chapter 29. In addition, radiographic identification of extracardiac disease can provide important prognostic information.[34a]

RADIOGRAPHIC APPEARANCE. The classic radiographic appearance of chronic, severe pericardial effusion is that of a large, round heart shadow, lacking an apex or other structural detail[2, 35] (Fig. 7–13; see also Figs. 29–6, 29–16). As a point of differentiation from general cardiomegaly due to heart disease, the left atrium is not prominent when moderate to severe pericardial effusion is present.

Acute pericardial effusion (e.g., left atrial rupture) may cause life-threatening cardiac tamponade, but it may result only in mild to moderate enlargement of the cardiac silhouette, making radiographic diagnosis uncertain. In chronic effusive states, severe fluid buildup and pericardial distention may result in severe, generalized rounding of the cardiac silhouette. Echocardiography is indicated to characterize cardiac anatomy and search for neoplasia and other causes of pericardial effusion.

Pericarditis may cause pericardial effusion. However, it may not always result in sufficient pericardial distortion so that cardiomegaly is detected by radiography.

CONGENITAL PERICARDIODIAPHRAGMATIC HERNIA

CLINICAL CAUSE. As a developmental abnormality, the pericardium adapts to the additional volume imposed by the presence of abdominal organs within the sac. Frequently, unexpected diagnosis is related to gastrointestinal or respiratory signs.[36]

RADIOGRAPHIC APPEARANCE. The diagnosis is suspected when the heart shadow is enlarged, is slightly distorted, and blends in with the diaphragm (*silhouette sign*). Radiographic evidence suggesting that abdominal organs are contained within the pericardial sac include (1) irregular, lucent areas caused by omental fat, (2) gas bubbles indicating entrapped stomach or intestines, and (3) cranially displaced or absent stomach, spleen, or other organs (see Fig. 29–6). Acute gastric or intestinal displacement occasionally causes obstructive ileus with dilated intestines.

Diagnosis is best confirmed by echocardiography or abdominal ultrasound. Alternative diagnostic techniques include peritoneography (inject 2 ml/kg of water-soluble contrast medium into the peritoneal cavity, roll the patient to disperse the contrast, and radio-

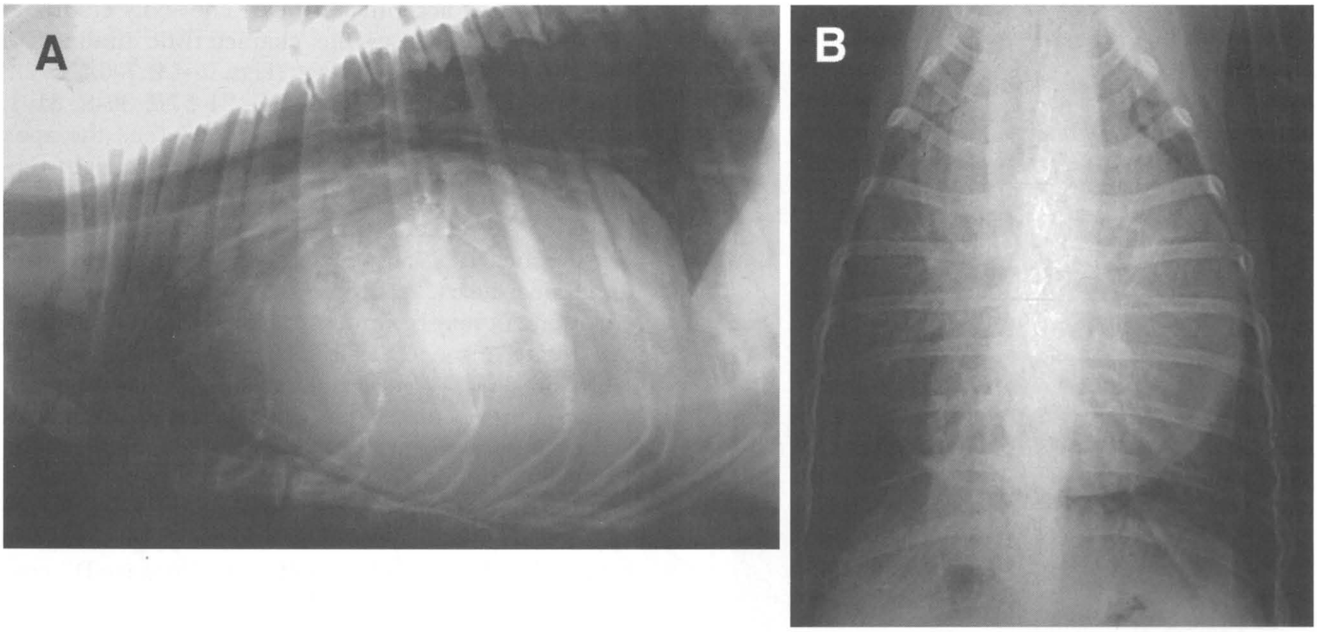


FIGURE 7–13

Lateral (A) and ventrodorsal (B) views of a dog with severe pericardial effusion. The cardiac silhouette is extremely large and round; the magnitude of this cardiomegaly is much greater than could be expected from valvular regurgitation or myocardial disease. Notice also that there is no distinctive cardiac chamber enlargement (i.e., the left atrium is not prominent), and the lungs are hypovolemic, lending support for pericardial effusion.

graph the thorax) and upper gastrointestinal contrast studies.

GREAT VESSELS AND MEDIASTINAL STRUCTURES

CHANGES IN GREAT VESSELS

CLINICAL CAUSE. The great vessels enlarge in response to increased pressure load or turbulence.[2, 22, 37–39] Stenosis of the pulmonary or aortic valve region causes poststenotic enlargement of the pulmonary trunk and aortic arch, respectively (chapter 24). However, absence of this detectable enlargement does not exclude semilunar valve stenosis when other appropriate auscultatory and clinical findings are present. Echocardiography and Doppler echo studies are confirmatory. When vascular blood flow is reduced by an intracardiac shunt, the vessel may be small or hypoplastic. This is usually observed in the pulmonary artery with tetralogy of Fallot owing to right-to-left shunting across a large ventricular septal defect.

RADIOGRAPHIC APPEARANCE. Appreciation of vascular changes is maximized when two well-positioned radiographic views are compared.

ENLARGED PULMONARY TRUNK. In the lateral view, the pulmonary trunk is normally not projected outward from the heart (Fig. 7–1*B*) and thus is not visible on plain radiographs unless severely enlarged. It may then appear as an anteriorly oriented, convexly shaped cap bulging forward and upward, superimposed on the trachea (see also Figs. 24–8*A*, 24–10, 24–28*B*; 30–8*B*; 31–3*A*).[37] In the VD/DV view, the main pulmonary trunk normally fills the cardiac border at the 1 to 2 o'clock position (Fig. 7–1*C*). A prominent bulge at this point most likely represents an enlarged pulmonary trunk caused by pulmonic stenosis (Figs. 7–10*B*, 7–12; see also Fig. 30–8*B*) or pulmonary hypertension. This bulge is not common with feline dirofilariasis,[40, 41] although it may occur occasionally (see Fig. 31–3). Rarely, enlarged mediastinal lymph nodes can create a similar bulge.

ENLARGED AORTIC ARCH. The aortic arch is not entirely constant in size. There is considerable variation in the normal curvature of the aortic arch in the dog and its appearance over the left cardiac border in the VD/DV view.[2, 15] It may also be displaced by neoplasia, especially heart-base tumors.

In the VD/DV view, it may fill the angle formed by the right atrial appendage and the cranial vena cava at 11 o'clock, bulging into the mediastinum and filling the angle between the cranial mediastinum and the pulmonary trunk at the 1 o'clock position (Fig. 7–14*B*; see also Fig. 24–17*A*).[2, 13, 15, 38] In old cats, a prominent bump may appear on the left border of the cranial mediastinum on the VD/DV projection, which is formed by the aortic arch viewed end-on. An enlarged aortic arch can be differentiated from a bulging pulmonary trunk in this view in that the lateral border of the aortic arch continues down the mediastinum just to the left of the spine, whereas the pulmonic bulge does not. In patent ductus arteriosus, the aorta is dilated at the point of exit from the ductus.[2, 22, 42] The dilation is best seen on a perfectly straight VD or DV view as a slight bulge on the left side of the aortic

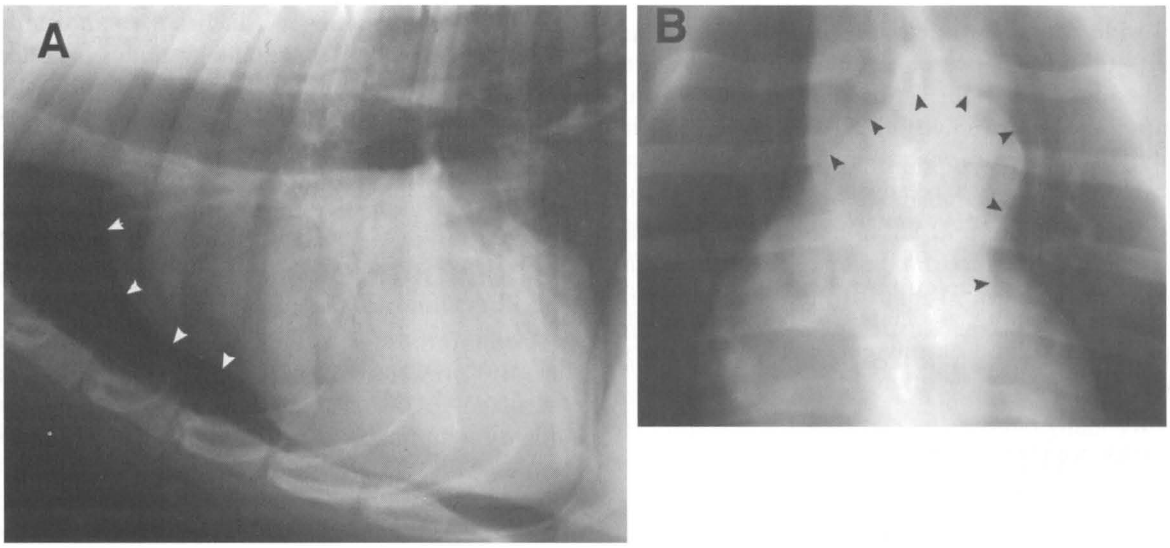


FIGURE 7–14

(A) Right lateral and (B) ventrodorsal views of a dog with congenital subaortic stenosis. Notice the poststenotic dilation of the aortic arch *(arrowheads)*.

FIGURE 7–15

Ventrodorsal view of a 6-year-old papillon with exercise intolerance, cyanosis during exercise, and no auscultatable cardiac murmur. Notice a prominent bulge *(arrowheads)* on the left side at the 2 o'clock position, representing the pulmonary trunk, and the aortic bulge above it at the 1 o'clock position. This pattern is diagnostic for patent ductus arteriosus, in this case with pulmonary hypertension. Two-dimensional echocardiography showed that the right ventricle and outflow tract were enlarged.

border, just caudal to the arch (Fig. 7–15; see also Fig. 24–42*A*).

In the lateral view, poststenotic dilation due to aortic stenosis extends into the cranial mediastinum. It fills in the angle formed by the cranial vena cava and the cranial heart border (Fig. 7–14*A*; see also Figs. 24–17*B*, 24–22) and increases the cranial mediastinal density.

CAUDAL VENA CAVA. In the lateral view, the position and angle of the caudal vena cava provides a clue to the size of the heart since it is elevated cranially if either ventricle is enlarged (Figs. 7–5, 7–9*A*). A persistently full and wide caudal vena cava, especially when combined with other evidence of cardiac decompensation, provides evidence of right ventricular failure, pericardial tamponade, constrictive pericarditis, or right atrial obstruction by an intracavitary neoplasm or thrombus.[2, 42a] However, it is a relatively insensitive sign of venous hypertension.[15, 43] A persistently thin cava (Fig. 7–3) is associated with poor venous return, hypovolemia, or increased intrapleural pressure. The latter is caused by air trapping associated with overinflation, asthma, bronchitis, and emphysema (which also cause radiographic signs of overinflated lungs).[2]

OTHER MEDIASTINAL STRUCTURES AND DISEASES

Lesions in this region are usually poorly defined. This results from the many mediastinal vessels and structures that are superimposed on each other and surrounded by mediastinal connective tissue.

PERIHILAR AND HEART BASE MASSES

Hilar lymphadenopathy can result from mycotic or bacterial (including tuberculosis) infection, or neoplasia. This increases the soft tissue density around the carina and left atrium and can be mistaken for left atrial enlargement in the lateral view.[2] A significant radiographic difference between hilar lymphadenopathy and left atrial enlargement on the lateral view, however, is that the former opacity usually lies dorsal to the main stem bronchi, which are not elevated, or may be compressed downward when severely enlarged (Fig. 7–16). In contrast, the left atrium lies ventral to the carina, and, when severely enlarged, it elevates the caudal trachea (Fig. 25–7), which loses its normal caudoventral sloping over the cardiac base (compare Figures 7–1*A* and 7–3 with 7–4*A* and and 7–6) and elevates the left main stem bronchus (Figs. 7–5, 7–6).

Very dilated main pulmonary arteries from pulmonary hypertension (especially severe dirofilariasis) cause a hilar opacity in the lateral view (Fig. 7–11). The trachea may be displaced or compressed in these instances.

The great vessels and trachea can also be displaced by heart base tumors (chemodectoma, aortic body tumors), infiltrating primary bronchogenic carcinoma, and right atrial hemangiosarcoma. Typically, these masses will elevate the trachea over the cranial mediastinum or heart base but not over the left atrium. They may also cause soft tissue density bumps or opacities around the heart base, often associated with pericardial effusion, tamponade, or caval obstruction.[2] Two-dimensional echocardiography is the preferred method for evaluating cardiac masses and pericardial effusion. Additional imaging techniques include a vena cavagram or selective angiography to outline intracavitary masses or obstructions[42a, 44]; pneumopericardiography to reveal right atrial masses[2, 45]; or computed tomography and magnetic resonance imaging.

THE ESOPHAGUS

Common radiographic findings in dyspneic animals are the presence of air throughout the esophagus or localized in the cranial thoracic region of a slightly dilated esophagus. An enlarged heart will compress the esophagus slightly and displace it dorsally.

Vascular ring anomalies cause esophageal stenosis with secondary dilation in the cranial mediastinum (see Fig. 24–61). Aspiration pneumonia may be present. A wide spectrum of vascular ring anomalies has been described (see Fig. 1–4; chapter 24). Persistent

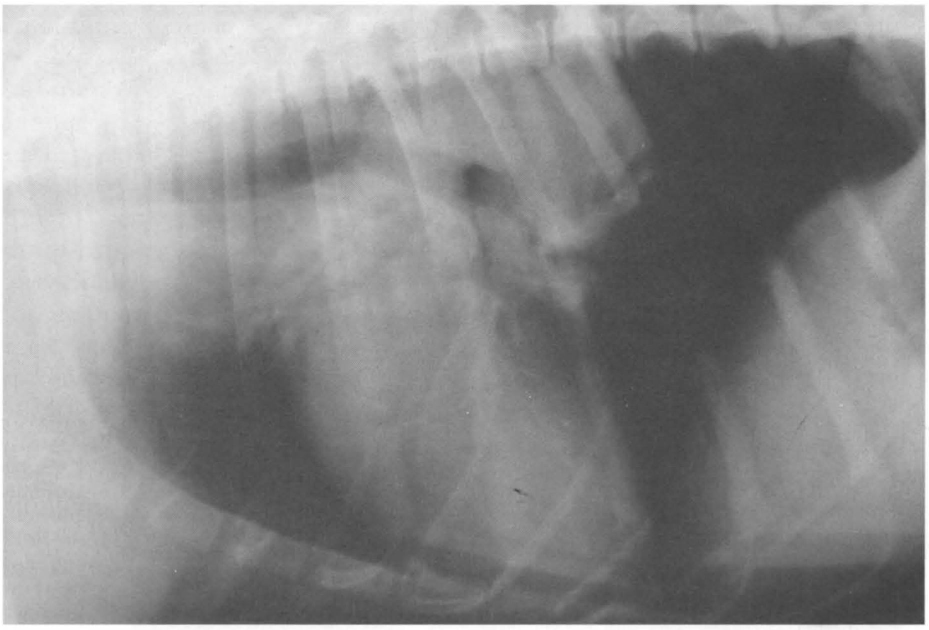


FIGURE 7–16

Right lateral radiograph from a coughing dog. Notice the severe hilar lymphadenopathy that causes acute ventral displacement of the distal trachea. The caudal cardiac border is relatively convex and normal. Tuberculosis was detected in hilar lymph nodes at necropsy. (Courtesy of Dr. Philip Fox.)

right aortic arch,[46] also called dextroaorta with left-sided ligamentum arteriosum, is the most prevalent type in dogs and cats. Severe tracheal compression and malformed tracheal rings are evidence of double aortic arch.[47] Persistent left cranial vena cava also may be present.[2]

TRACHEA AND MAIN BRONCHI

In the lateral view, the position of the caudal trachea relative to the spine provides an indication of the presence and severity of cardiomegaly, especially left-sided. A distal trachea displaced upward toward the spine suggests a large heart (e.g., severe pericardial effusion; dilated cardiomyopathy) or moderate to severe left atrial and ventricular enlargement. In particular, dorsal displacement and compression of the left main stem bronchus indicates left atrial enlargement. The position of the trachea and main stem bronchi helps differentiate left atrial enlargement from other causes of hilar disease (see earlier section on Perihilar and Heart Base Masses).[2]

Tracheal collapse is often present in conjunction with chronic acquired valvular disease (endocardiosis) in small-breed dogs (chapter 25). Radiologic examination often helps clarify or resolve the cause of coughing (Fig. 7–17). In dogs with large airway disease, the trachea typically collapses in the cervical or the thoracic regions, or both. The cervical (extrathoracic) trachea collapses during inspiration. The intrathoracic trachea collapses during expiration. Upper airway obstruction by an elongated or swollen soft palate will exaggerate cervical tracheal collapse. Exposing lateral radiographs during both expiration and inspiration will increase diagnostic accuracy to confirm tracheal collapse.[2] On routine inspiratory radiographs made of the heart, intrathoracic tracheal collapse may not be manifested.

Compression or collapse of the left main stem bronchus often accompanies collapsed trachea or severe left atrial enlargement in dogs (Fig. 7–6). Coughing from bronchial compression may be mistaken for a cough due to pulmonary congestion and requires evaluation of other clinical and diagnostic findings (chapters 4 and 5).

THE LUNG FIELD IN HEART DISEASE

The pulmonary radiograph has been likened to a window reflecting underlying cardiopulmonary pathophysiology. Evaluation of lung fields often provides more useful information than determination of cardiac chamber size. It helps in assessing the severity of the hemodynamic disturbance (i.e., congestive heart failure), and the effects of therapy. Air in the small airways and alveoli acts as a contrast medium outlining the pulmonary vessels and parenchyma. This makes radiography a relatively sensitive and specific method of assessing the pulmonary vascular circulation. Since this natural contrast fluctuates with the phase of respiration (Fig. 7–17), a false diagnosis of pulmonary edema can be made when evaluating expiratory radiographs.

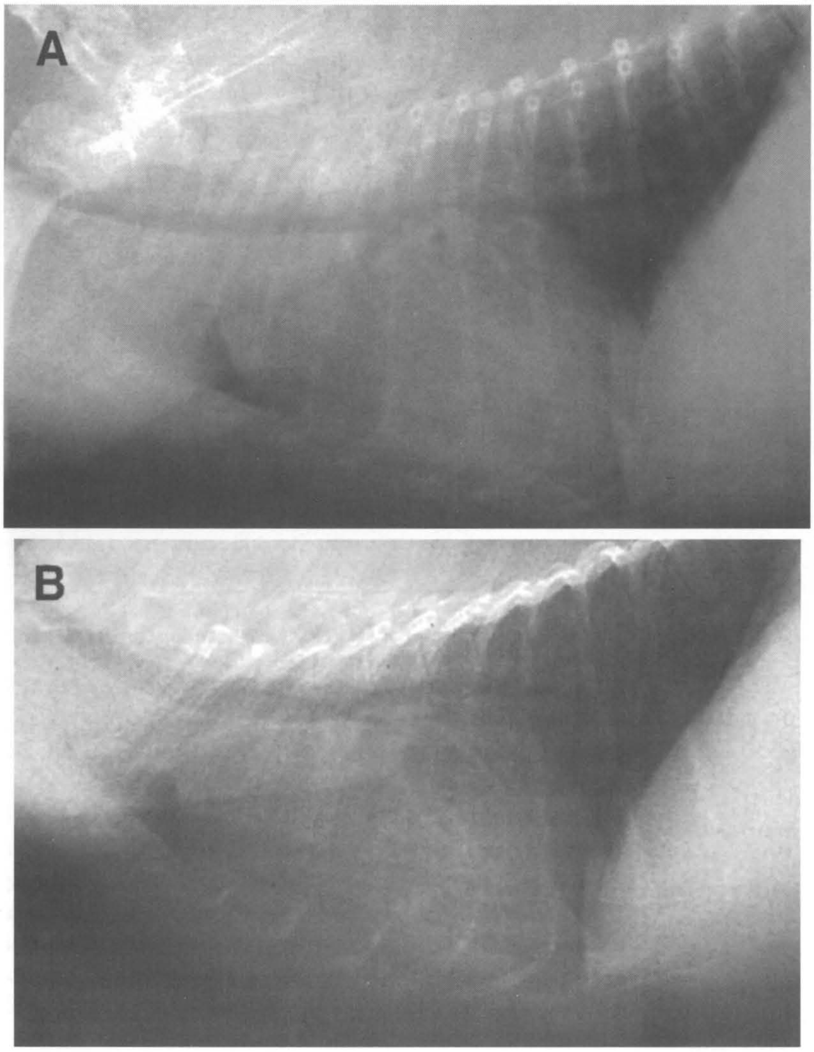


FIGURE 7–17

Right lateral radiographs from an 11-year-old Yorkshire terrier with a chronic cough and chronic mitral regurgitation. At expiration (A), the intrathoracic trachea is relatively collapsed, and the dorsal lungs have a diffuse opacity. The heart overlies the diaphragm. At inspiration (B), the trachea is normal in diameter, and the lung fields are clear. On both films, there is mild left atrial enlargement and severe right ventricular enlargement. Coughing was caused by the large airway disease (collapsed trachea).

NORMAL VARIATIONS

Care must be exercised when interpreting radiographs exposed under different conditions. For example, thick thoracic walls in an obese animal may impart a uniform gray opacity to the radiographs because of scattered radiation, especially in the lateral view of small, round-chested dogs. One must also interpret films made under general anesthesia cautiously. The dependent lung may be underinflated or both lungs may be underinflated, creating false opacity after only a few minutes of lateral recumbency. Under- or overinflated lungs warrant special consideration.

UNDERINFLATED LUNGS. Conditions that increase radiographic lung opacity and decrease diagnostic quality include (1) reduced tidal volume from obesity; (2) conditions restricting lung inflation; and (3) cranially displaced diaphragm from increased abdominal pressure compressing the lungs and preventing good inflation (hepatomegaly, obesity, large masses, or ascites).

OVERINFLATED LUNGS. Overinflation of the lungs by mechanical ventilation may eliminate pulmonary infiltrates, such as pulmonary edema, by creating artificial pulmonary lucency. Ideally, a physiologic end-expiratory pressure should be maintained.

THE VASCULATURE

HYPERPERFUSION (OVERCIRCULATION). Hypervascularity results from significantly increased pulmonary blood flow (two or more times normal). Causes include (1) left-to-right shunting (central or peripheral); (2) hyperdynamic states such as chronic, severe anemia or thyrotoxicosis; and (3) iatrogenic volume overload or congestive heart failure.[1, 2] Hyperdynamic states that are often not radiographically apparent cause relatively mild overcirculation. Large left-to-right shunts may eventually cause a pressure overload (and enlargement) on the right ventricle if pulmonary vascular resistance rises.[22, 27, 28, 42]

Normally, only a small proportion of the pulmonary capillary bed is perfused. Greater flow causes more capillaries to be recruited. Increased numbers of perfused vessels reduce contrast of lung parenchyma against the vessels. This creates a hazy increase in interstitial opacity resembling interstitial pulmonary edema (chapter 13). These conditions are indistinguishable. However, the distribution of hypervascularity is more widespread in states of overcirculation, and vascular markings extend to the lung periphery, as opposed to cardiac interstitial edema, which is more central in distribution with less prominent vascular markings.

Overcirculation is best appreciated in the lateral view (Fig. 7–18; see also Fig. 24–28*B*; 24–36, 24–42*B*), in which the arteries and veins are prominent and widened due to increased flow and pressure. When cardiovascular shunts are present, their location may be suggested by cardiac radiographic changes (chapter 24).

HYPOPERFUSION (UNDERCIRCULATION). Causes of generalized hypoperfusion include (1) right-to-left shunts; (2) low cardiac output (e.g., shock or severe myocardial failure, severe dehydration, acute adrenocortical insufficiency, restrictive pericarditis, caval or right atrial obstruction, cardiac tamponade, severe right heart failure, complete heart block); or (3) severe emphysema.[1, 2] Technical faults involving radiographic technique or processing may create images that resemble undercirculation. Examples include overexposure, overdevelopment, or overinflation (due to struggling or upper airway obstruction). Overinflation can be recognized by a flat diaphragm on the lateral view and wide costodiaphragmatic angles in the VD or DV views.

Radiographic findings of hypoperfusion include thin pulmonary arteries and veins and a relatively radiolucent interstitium (Fig. 7–3; see also Fig. 24–7). These changes when interpreted in conjunction with other clinical abnormalities may help in formulating a diagnosis. Hypoperfusion with right ventricular enlargement but without an enlarged main pulmonary artery suggests tetralogy of Fallot or Ebstein's anomaly; hypoperfusion with a generalized, rounded cardiac silhouette will be present when pericardial effusion causes cardiac tamponade.[45] Isolated pulmonic stenosis has been reported to cause an underperfused lung field, even in clinically normal dogs.[37] Whether the appearance reflects true hypoperfusion, hyperlucency due to other causes, or interpretive bias (i.e., belief that pulmonic stenosis should cause hypoperfusion) is unresolved.

Lobar hypoperfusion is compatible with pulmonary thromboembolism.[39] Additional radiographic signs of thromboembolism include thin pulmonary veins, pleural effusion, proximally dilated pulmonary artery in the affected lobe and elsewhere, and right ventricular enlargement.

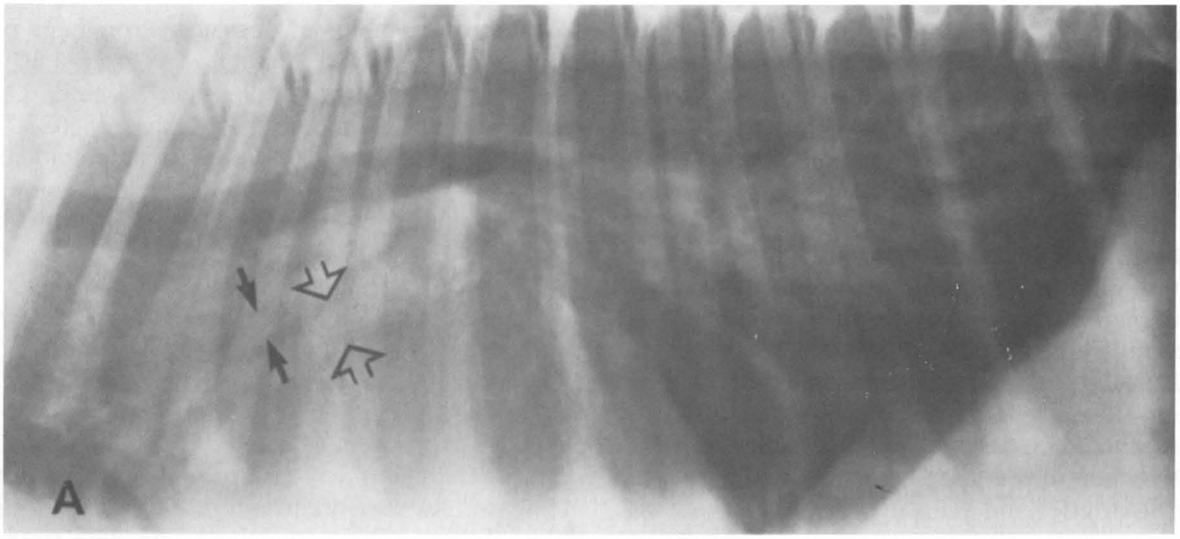
PROMINENT PULMONARY ARTERIES. Prominent pulmonary arteries are a sign of pulmonary arterial hypertension. Pulmonary hypertension may be acute (e.g., pulmonary thromboembolism), or chronic (e.g., some left-to-right shunts, chronic obstructive pulmonary disease, and chronic hypoxia). The most common cause of pulmonary hypertension is canine heartworm disease.

The location of pulmonary arteries is predictable, and radiographic changes are often dramatic.[39, 48, 49] In the lateral view, the cranial arteries lie dorsal to the veins and can usually be seen even when the caudal vessels are obscured by perivascular inflammatory infiltration. With pulmonary hypertension, the proximal arteries become wide and the middle portions become tortuous. The peripheral sections are usually thin. Enlargement is indicated when the relative size of the right cranial pulmonary artery exceeds 1.2 times the width of the right fourth rib at a point just below the spine.[50] In the VD/DV view, the pulmonary arteries are lateral to the pulmonary veins.

CANINE HEARTWORM DISEASE (chapter 30). Slight irregularities and tortuosity of the right main caudal artery are the most sensitive signs of mild early dirofilariasis (Fig. 7–19).[51, 52] At this stage the heart is normal, and there is no visible perivascular reaction. Pulmonary arterial changes accompanying dirofilariasis include (1) enlargement, (2) indentation or scalloping, (3) tortuosity, (4) disappearance, (5) pruning, and (6) serration[2, 52] (see Figs. 30–5, 30–6, 30–8). To maximize the chance of recognizing these subtle changes, particularly in vessels that overlie the liver, a DV view with good lung inflation is necessary.[52]

Periarterial inflammatory lesions and edema often make the vessels difficult to identify, particularly in the lateral view. The classic signs of enlarged right ventricle and main pulmonary artery may be obscured. Under these conditions, severe heartworm lesions may be confused with pulmonary neoplasia because the grossly enlarged and distorted arteries, when viewed end on, resemble lung masses. This error is particularly likely if only a lateral view is taken on which the main caudal arteries are superimposed. The accompanying changes in the right ventricle and pulmonary trunk are less likely to be visible on the lateral than on the DV view.

FELINE HEARTWORM DISEASE (chapter 31). In the cat, diagnosis of heartworms requires careful inspection of the main caudal pulmonary arteries, particularly the left caudal pulmonary artery,[52a] seen best in the DV or DV oblique views[40, 53] (see Figs. 31–3, 31–4). The worms may be obscured by interstitial inflammatory infiltrate. Compared with dogs, arteritis is less evident, and worms are fewer and smaller in cats. Typically, pulmonary hypertension is not severe enough to cause a prominent pulmonary trunk.[41] Nonselective angiogra-



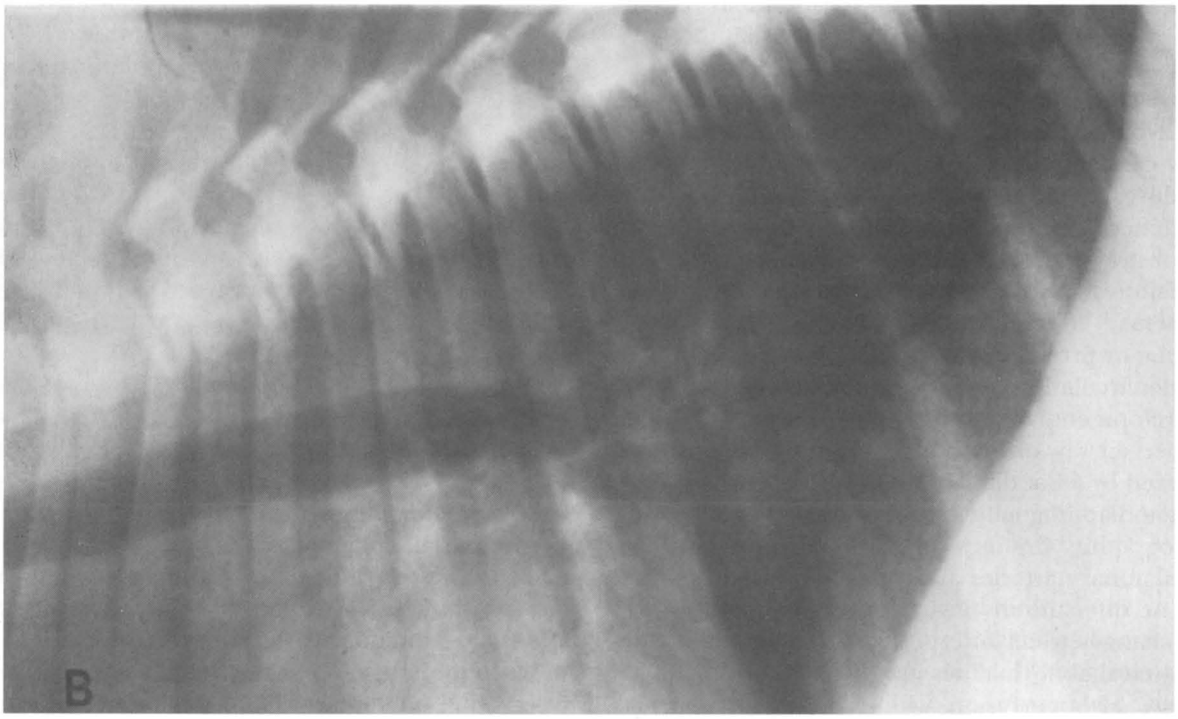


FIGURE 7–18

Right lateral thoracic radiograph of a pair of 2-month-old golden retriever littermates. (A) Hyperperfused, overcirculated lungs are caused by a left-to-right shunting patent ductus arteriosus. Note the engorged distended pulmonary veins *(open arrows)* overlying the cardiac silhouette. Pulmonary arteries *(closed arrows)* are also abnormally wide and are best visualized in the cranial lung lobes. There is a diffuse, interstitial pulmonary density, especially evident in the perihilar region, due to overcirculation. The left atrium is enlarged and elevates the trachea. Compare these changes with those in the normal littermate (B).

phy (see Fig. 31–4) and serology may be necessary for diagnosis.[40, 54]

PROMINENT PULMONARY VEINS. Pulmonary veins lie medial to the pulmonary arteries on the VD/DV view; in the lateral view, they lie ventral to the cranial lobar bronchi (the order of distribution from dorsal to ventral is pulmonary artery, bronchus, and pulmonary vein, respectively).[1, 2] Pulmonary venous hypertension is usually caused by chronically elevated left ventricular filling pressure, as occurs in dogs with chronic acquired degenerative mitral valve disease (endocardiosis, chapter 25). It may also develop acutely in decompensated canine dilated cardiomyopathy or in feline cardiomyopathy. These changes are always associated with moderate to severe left atrial enlargement.

FIGURE 7–19

Ventrodorsal view of a dog with heartworm disease. Notice the wide and tortuous main caudal pulmonary arteries.

Not all cases of left-sided heart failure have pulmonary venous enlargement evident on radiographs, however. Moreover, pulmonary edema may obscure venous engorgement when present in some cases.

Chronic pulmonary venous hypertension often results in distended and tortuous pulmonary veins (Fig. 7–20; see also Figs. 13–2; 24–17*B*, 24–28*B*). They may sometimes be identified on a DV view with the lungs well inflated. Dilated cranial veins may also be visible in the lateral view. Distention is greatest in the perihilar area, where the veins are widest and wall tension (according to the law of Laplace) is highest at any given venous pressure.

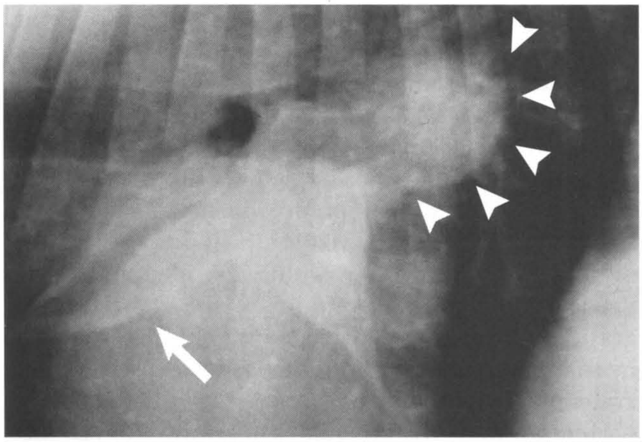


FIGURE 7–20

Right lateral view of a dog with heart failure from chronic acquired mitral regurgitation (endocardiosis), showing pulmonary venous congestion. Proximal pulmonary veins *(arrow)* are greatly dilated over the heart. The left atrium is severely enlarged *(arrowheads)* from chronic mitral regurgitation. No pulmonary edema has yet developed.

PULMONARY PARENCHYMA

INTERSTITIAL PULMONARY EDEMA

The interstitium is an extravascular tissue compartment that expands to accommodate excess transudated fluid, which is then drained by pulmonary lymphatics (chapter 13). When this process is overwhelmed, interstitial pulmonary edema may occur as a uniform, poorly defined increase in lung opacity that reduces small vessel sharpness or clarity (Fig. 7–6; see also Figs. 13–4, 13–5; 24–42).

Whether interstitial pulmonary edema can be diagnosed radiographically depends on technical factors, including lung inflation. Films that are exposed at expiration may mimic this finding. Ideally, comparison of serial radiographs exposed with similar technique and phase of inspiration should be made.

ALVEOLAR PULMONARY EDEMA

Alveolar pulmonary edema represents a more advanced state of left ventricular failure than interstitial edema. It is characterized by absence of pulmonary air contrast, the air being replaced by alveolar edema fluid. If sufficiently severe, the edema obscures vascular markings (see Figs. 13–2 to 13–5 and 25–5). The bronchi are not flooded and may show up as radiolucent *air bronchograms* (see Figs. 13–2 to 13–6; 24–17; 25–5; 28–11). In the lateral view, air bronchograms appear as tapering and branching thick, radiolucent lines surrounded by opacity, obscuring adjacent vessels.[2] In the VD/DV view, air bronchograms are often shorter or appear as round, lucent "holes." This is because in this view the bronchi are foreshortened or appear end on.

An alternative appearance for acute pulmonary edema is a finely stippled or fine nodular pattern. This *air alveologram* pattern is caused by groups of fluid-filled (opaque) acini mixed with air-filled (lucent) acini or alveoli.

Many other conditions besides left ventricular failure, such as pneumonia and hemorrhage, cause an acute alveolar pattern. The radiographic distribution of infiltrates is helpful in formulating a diagnosis.[1, 2, 55] For cardiogenic pulmonary edema in the dog, the most common distribution is dorsal, perihilar, and symmetric. There may also be pulmonary venous engorgement and moderate to severe left heart enlargement. By contrast, pneumonia is typically peribronchial, lobar, cranial, and ventral in distribution, without concomitant cardiomegaly (unless unassociated cardiac disease happens to be coincidentally present). Therefore, it is usually possible to differentiate these two

common causes of dyspnea by radiographs. Although acute, fulminant pulmonary edema may extend into the cranioventral lung field, it will always have a predominant perihilar component. Pulmonary edema secondary to chronic mitral regurgitation is often accentuated in the right caudal lobe.[2]

In cats with hypertrophic or restrictive cardiomyopathy, pulmonary edema is usually patchy and asymmetrically distributed; the air alveologram pattern predominates. Perihilar distribution is rare. Moderate to severe left auricular enlargement is usually clearly evident on the DV/VD view. Bronchopneumonia in cats appears similar to that in dogs but is much less common.

Early pulmonary edema as a sign of left ventricular failure occasionally may be masked by other factors. Overinflated lungs will reduce the radiographic density of pulmonary edema. This may occur by forced inspiration during the stress of manual restraint associated with radiographic positioning, or if an animal is ventilated under general anesthesia. Severe right ventricular failure accompanying left ventricular failure may decrease pulmonary perfusion pressure as well as obscure visualization of pulmonary parenchyma.

PULMONARY FIBROSIS

Pulmonary fibrosis causes a diffuse interstitial opacity that may be indistinguishable from poor lung inflation or pulmonary edema.[2] Since pulmonary fibrosis is associated with chronic obstructive pulmonary disease caused by chronic bronchitis and tracheal and bronchial collapse, diagnosis in small dogs with chronic cough and concurrent mitral regurgitation may sometimes be difficult from radiographs unless clinical findings are carefully evaluated.

FOCAL PULMONARY LESIONS ASSOCIATED WITH HEART DISEASE

Focal pulmonary lesions may occur with certain cardiovascular disorders. Dirofilariasis causes severe lung reactions.[2, 48, 49] Lesion distribution may range from patchy or diffuse interstitial patterns in occult heartworm disease to lung consolidation caused by thrombosis following adulticide treatment (see Figs. 30–5, 30–7, 30–10). Eosinophilic pulmonary granulomas may be present. The pulmonary pattern in cats with dirofilariasis is usually much milder. Patchy interstitial and alveolar densities have been reported (see Figs. 31–1, 31–2).[40, 41, 53]

Acute pulmonary thromboembolism in dogs as a complication of systemic diseases is manifested in a variety of focal pulmonary lesions (Fig. 30–11). They include single or multiple alveolar opacities, lobar collapse, and asymmetric lucency because of oligemia in the affected lung or lobe.[39]

Bacterial endocarditis may cause septic pneumonia and thromboembolism as well as pulmonary edema. The pulmonary lesions may be difficult to differentiate. Consolidated areas may be present due to embolization.[2] Pulmonary metastases may also be associated with hemangiosarcoma[34] or heart base tumors.

THE PLEURAL CAVITY

Diseases involving the pleura and pleural space may be subdivided into those that cause (1) increased radiographic pleural and thoracic density (i.e., pleural effusion, pleural masses, and pleural thickening), and (2) those that result in diminished pleural and thoracic density (i.e., pneumothorax).[2]

In heart failure, two radiographic signs of pleural involvement may be observed. The most common abnormality is pleural effusion that follows right-sided heart failure either (1) directly from a right-sided heart volume overload (e.g., tricuspid regurgitation) or pressure overload, (2) from severe left-sided heart disease (e.g., advanced mitral regurgitation or hypertrophic cardiomyopathy, (3) from generalized heart failure (e.g., dilated cardiomyopathy), or (4) conditions associated with ventricular underfilling, such as cardiac tamponade or constrictive pericarditis. In constrictive pericarditis, the heart shadow is not usually enlarged.[56] In dogs, pleural effusion usually follows liver congestion and ascites in the progression of signs. In cats, pleural effusion may accompany all forms of decompensated cardiomyopathy, especially myocardial failure. A complete data base is often required to differentiate cardiogenic and noncardiogenic pleural effusion. The least common pleural cavity abnormality is pleural thickening or pleural edema. It is caused by acute, severe left ventricular failure that overwhelms the pulmonary lymphatic drainage and always occurs with acute alveolar edema.

The radiographic signs of pleural effusion have been described in detail.[2] Differences in its appearance between the VD and DV views are important in heart disease. Free fluid moves within the pleural cavity by gravity. In the prone position for the DV view, fluid gravitates to the ventral regions and surrounds the heart and diaphragm. In the DV view, even small amounts of pleural effusion may obscure the cardiac silhouette and diaphragm. Therefore, a VD view should be taken if possible, since in the supine position fluid gravitates away from the heart and diaphragm to the dorsal regions of the pleural cavity (see Fig. 28–19).[2, 8] Alternatively, in severe hydrothorax, initial thoracocentesis and drainage will relieve dyspnea and ensure better visualization of thoracic organs.

THE ABDOMEN

Thoracic radiographs should include the cranial abdomen. Liver enlargement and ascites are general sequelae of right-sided or generalized congestive heart failure. When congenital peritoneodiaphragmatic pericardial hernia is suspected, diagnosis is supported by an enlarged, rounded cardiac silhouette and missing or cranially displaced abdominal organs (see Fig. 29–6). Moreover, radiographic evaluation of the abdomen may reveal noncardiac causes of abdominal effusions such as neoplasia.

Liver enlargement is often radiographically overdiagnosed. Standard criteria for normal liver size state that the caudoventral tip should lie at the costal arch. However, the liver moves beyond the arch in inspiration, particularly if the thorax is expanded and the diaphragm is flat, as with dyspnea or pleural effusion. Hepatomegaly results from many noncardiac diseases and is not uniformly present in heart failure.

DIAGNOSIS OF CONGENITAL HEART DISEASE

The heart and lungs should always be interpreted together. A scheme for their evaluation in congenital heart disease illustrates how diagnoses of common specific disorders can be made from plain films (Table 7–2). The addition of clinical signs often enables a specific diagnosis to be made.

In addition to assisting diagnosis of a particular congenital anomaly, the radiologic examination offers a prognostic guide for some conditions, particularly those with volume overload, by revealing the severity of cardiomegaly and its hemodynamic consequences. Plain film radiography is reasonably accurate for diagnosing some congenital anomalies such as patent ductus arteriosus. This accuracy is greatly increased when assessed in conjunction with clinical findings. However, echocardiography, including color-flow and spectral Doppler echocardiography, is required for definitive diagnosis and characterization of most congenital diseases. When diagnostic ultrasound is unavailable, the patient can be referred for echocardiography or cardiac catheterization. Occasionally, nonselective angiocardiography may help delineate some disorders.[57]

CONCLUSIONS FROM THE RADIOGRAPHIC EXAMINATION

The astute clinician will evaluate radiologic signs of cardiopulmonary disease within the context of an insightful history and a complete clinical data base.

TABLE 7–2
Diagnostic Scheme for Congenital Heart Diseases

Lung Field	Congenital Cardiac Anomaly	Cardiac Silhouette
Underperfused	Severe pulmonic stenosis Tricuspid dysplasia Tetralogy of Fallot Pulmonic stenosis with atrial septal defects (R → L shunt)	Right side enlarged (or usually enlarged)
Prominent pulmonary veins	Aortic stenosis in left ventricular failure Mitral valve malformation or stenosis	Left side enlarged
Prominent arteries and veins (overperfused)	Atrial septal defects (L → R shunt) Ventricular septal defects (L → R shunt) Patent ductus arteriosus (L → R shunt) Arteriovenous shunts (L → R shunt)	Generally enlarged
Prominent pulmonary arteries	Eisenmenger's syndrome (hypertensive, R → L shunting, VSD, PDA, ASD)	Variable cardiac enlargement
Normal	Pulmonic stenosis (mild) Pulmonic or tricuspid incompetence Small ventricular septal defect	Right side enlarged
	Aortic stenosis (severe) Compensated congenital mitral valve malformation	Left side enlarged
	Multiple defects Peritoneodiaphragmatic pericardial hernia	General enlargement
Edema	Left ventricular failure Biventricular failure	Variable cardiac enlargement

VSD, ventricular septal defect; PDA, patent ductus arteriosus; ASD, atrial septal defect.

The accuracy of assessing minor degrees of cardiac chamber enlargement is questionable.[2, 18] Radiologic and echocardiographic assessment do not always correlate. Also, for evaluation of cardiac morphology, radiography is more sensitive than some diagnostic tests (e.g., for left atrial and right ventricular enlargement compared with the ECG[58, 59]), but it is less accurate than echocardiography. In contrast, there is no substitute for radiography for assessing lung fields and pleural cavity and providing an overall balanced assessment for thoracic and cardiorespiratory diseases. Radiographic information must be carefully assessed, together with clinical findings and other diagnostic tests, for reliability, sensitivity, specificity, and prognosis. Different diagnostic tests are used to complement each other. Computer algorithms have not yet replaced the educated and prepared mind.

REFERENCES

1. Burk RL, Ackerman N. Small Animal Radiology and Ultrasonography. Philadelphia, WB Saunders, 1996
2. Suter PF, Lord PF. Thoracic Radiography: Thoracic Diseases of the Dog and Cat. Wettswil, Switzerland, PF Suter, 1984
3. Holmes RA, Smith GF, Lewis RE, Kern EM. The effects of rotation on the radiographic appearance of the canine cardiac silhouette in dorsal recumbency. Vet Radiol 26:98, 1985
4. Grandage J. The radiology of the dog's diaphragm. J Small Anim Pract 14:89, 1974
5. Ruehl WW, Thrall DE. The effect of dorsal versus ventral recumbency on the radiographic appearance of the canine thorax. Vet Radiol 22:10, 1981
6. Carlisle CH, Thrall DE. A comparison of normal feline thoracic radiographs made in dorsal versus ventral recumbency. Vet Radiol 23:3, 1982
7. Silverman S, Suter PF. Influence of inspiration and expiration on canine thoracic radiographs. J Am Vet Med Assoc 166:502, 1975
8. Groves TF, Ticer JW. Pleural fluid movement: Its effect on appearance of ventrodorsal and dorsoventral radiographic projections. Vet Radiol 24:99, 1983
9. van der Broek AHM, Darke PGG. Cardiac measurements on thoracic radiographs of cats. J Small Anim Pract 28:125, 1987
10. Moon ML, Keene BK, Lessard P, et al. Age related changes in the feline cardiac silhouette. Vet Radiol Ultrasound 34:315, 1993
11. Toal RL, Losonsky JM, Coulter DB, De Novellis R. Influence of cardiac cycle on the radiographic appearance of the feline heart. Vet Radiol 26:63, 1985
12. Rankin JS, McHale PA, Arentzen CE, et al. The three-dimensional dynamic geometry of the left ventricle in the conscious dog. Circ Res 39:304, 1976
13. Hamlin RL. Analysis of the cardiac silhouette in dorsoventral radiographs from dogs with heart disease. J Am Vet Med Assoc 153:1446, 1968
14. Buchannan JW, Bücheler J. Vertebral scale system to measure canine heart size in radiographs. J Am Vet Med Assoc 206:194, 1995
15. Suter PF, Lord PF. A critical evaluation of the radiographic findings in canine cardiovascular diseases. J Am Vet Med Assoc 158:358, 1971
16. Lord PF, Zontine WJ. Radiologic examination of the feline cardiovascular system. Vet Clin North Am 7:281, 1977
17. Hamlin RL, Smetzer D, Smith C. Radiographic anatomy of the normal cat heart. J Am Vet Med Assoc 143:957, 1963
18. Murphy ML, Blue LR, Thenabada PN, et al. The reliability of the routine chest roentgenogram for determination of heart size based on specific ventricular chamber evaluation at postmortem. Invest Radiol 20:21, 1985
19. Lord PF. Radiologic examination. *In* Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 91
20. Snyder PS, Sato T, Atkins CE. The utility of thoracic radiographic measurement for the detection of cardiomegaly in cats with pleural effusion. Vet Radiol 31:89, 1990
21. Fox PR. Feline cardiomyopathy. *In* Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 435
22. Ackerman N, Burk R, Hahn AW, Hayes HM Jr. Patent ductus arteriosus in the dog: A retrospective study of radiographic, epidemiologic, and clinical findings. Am J Vet Res 39:1805, 1978
23. Lord PF, Wood A, Tilley LP, Liu SK. Radiographic and hemodynamic evaluation of cardiomyopathy and thromboembolism in the cat. J Am Vet Med Assoc 164:154, 1974
24. Lord PF, Wood A, Liu SK, Tilley LP. Left ventricular angiocardiography in congenital mitral valve insufficiency of the dog. J Am Vet Med Assoc 166:1069, 1975
25. Lord PF. Left ventricular diastolic stiffness in dogs with congestive cardiomyopathy and volume overload. Am J Vet Res 37:953, 1976
26. Sisson D, Thomas WP. Endocarditis of the aortic valve in the dog. J Am Vet Med Assoc 184:570, 1984
27. Weirich WE, Blevins WE, Rebar AH. Late consequences of patent ductus arteriosus in the dog: A report of six cases. J Am Anim Hosp Assoc 14:40, 1978
28. Feldman EC, Nimmo-Wilki JS, Pharr JW. Eisenmenger's syndrome in the dog: Case reports. J Am Anim Hosp Assoc 17:477, 1981
29. Ware WA, Bonagura JD. Multiple congenital cardiac anomalies and Eisenmenger's syndrome in a dog. Can Vet J 10:932, 1988
30. Oswald GP, Orton EC. Patent ductus arteriosus and pulmonary hypertension in related Pembroke Welsh corgis. J Am Vet Med Assoc 202:76, 1993
31. Laks MM, Morady T, Garner D, Swan HJC. Relation of ventricular volume, compliance and mass in the normal and pulmonary artery banded heart. Cardiovasc Res 6:187, 1982
32. Weber KT, Janicki JS, Shroff SG. The right ventricle: Physiologic and pathophysiologic considerations. Crit Care Med 11:323, 1983
33. Liu S-K, Tilley LP. Dysplasia of the tricuspid valve in the dog and cat. J Am Vet Med Assoc 169:623, 1976
34. Holt D, Winkle T, Schelling C, et al. Correlation between thoracic radiographs and post mortem findings in dogs with hemangiosarcoma. J Am Vet Med Assoc 200:1535, 1992

34a. Dunning D, Monnet E, Orton C, et al. Analysis of prognostic indicators for dogs with pericardial effusion: 46 cases (1985–1996). J Am Vet Med Assoc 212:1276, 1998

35. Gibbs C, Gaskell CJ, Darke PGG, Wotton PR. Idiopathic pericardial hemorrhage in dogs: A review of 14 cases. J Small Anim Pract 23:483, 1982
36. Evans SM, Biery DN. Congenital peritoneopericardial diaphragmatic hernia in the dog and cat: A literature review and 17 additional case histories. Vet Radiol 21:108, 1980
37. Fingland RB, Bonagura JD, Myer CW. Pulmonic stenosis in the dog: 29 cases (1975–1984). J Am Vet Med Assoc 189:218, 1986
38. O'Grady MR, Holmberg DL, Miller GW, Cockshutt JR. Canine congenital aortic stenosis: A review of the literature and commentary. Can Vet J 30:811, 1989
39. Flukiger M, Gomez J. Radiographic findings in dogs with spontaneous pulmonary thrombosis or embolism. Vet Radiol 25:124, 1984
40. Green BJ, Lord PF, Grieve RB. Occult feline dirofilariasis confirmed by angiography and serology. J Am Anim Hosp Assoc 19:847, 1983
41. Donahue JMR, Kneller SK, Lewis RE. Hematologic and radiographic changes in cats after inoculation with infective larvae of *Dirofilaria immitis*. J Am Vet Med Assoc 168:413, 1976
42. Patterson OF, Pyle RL, Buchanan JW, et al. Hereditary patent ductus arteriosus and its sequelae in the dog. Circ Res 29:1, 1971
42a. Edwards DF, Bahr RJ, Suter PF, et al. Portal hypertension secondary to a right atrial tumor in a dog. J Am Vet Med Assoc 173:750, 1978
43. Thrall DE, Calvert CA. Radiographic evaluation of canine heartworm disease coexisting with right heart failure. Vet Radiol 24:124, 1983
44. Cantwell HD, Blevins WE, Weirich WE. Angiographic diagnosis of heartbase tumor in the dog. J Am Anim Hosp Assoc 18:83, 1982
45. Berg RJ, Wingfield W. Pericardial effusion in the dog: A review of 42 cases. J Am Anim Hosp Assoc 20:721, 1983
46. Shires PK, Liu WI. Persistent right aortic arch in dogs: A long-term follow-up after surgical correction. J Am Anim Hosp Assoc 17:773, 1981
47. Martin DG, Ferguson EW, Gunnels RD, et al. Double aortic arch in a dog. J Am Vet Med Assoc 183:697, 1983
48. Calvert CA, Rawlings CA. Pulmonary manifestations of heartworm disease. Vet Clin North Am 15:991, 1985
49. Ackerman N. Radiographic aspects of heartworm disease. Semin Vet Med Surg (Small Anim) 2:15, 1987
50. Thrall DE, Losonsky JM. A method for evaluating canine pulmonary circulatory dynamics from survey radiographs. J Am Anim Hosp Assoc 12:457, 1976
51. Losonsky JR, Thrall DE, Lewis RE. Thoracic radiographic abnormalities in 200 dogs with spontaneous heartworm infestation. Vet Radiol 24:120, 1983
52. Holmes RA. Techniques to aid in the radiographic diagnosis of heartworm disease. J Am Vet Med Assoc 1986:1063, 1985
52a. Atkins CE, DeFrancesca TC, Miller MW, et al. Prevalence of heartworm infection in cats with signs of cardiorespiratory abnormalities. J Am Vet Med Assoc 212:517, 1998
53. Dillon R. Feline dirofilariasis. Vet Clin North Am 14:1185, 1984
54. Wong MM, Pederson NC, Cullen J. Dirofilariasis in cats. J Am Anim Hosp Assoc 19:855, 1983
55. Burk RL. Radiographic examination of the cardiopulmonary system. Vet Clin North Am 13:241, 1983
56. Thomas WP, Reed JR, Gomez JA. Diagnostic pneumopericardiography in dogs with spontaneous pericardial effusion. Vet Radiol 25:2, 1984
57. Stickle RL, Anderson LK. Diagnosis of common congenital heart anomalies in the dog using survey and nonselective contrast radiography. Vet Radiol 28:6, 1987
58. Lombard CW, Ackerman N. Right heart enlargement in heartworm-infected dogs: A radiographic, electrocardiographic and echocardiographic correlation. Vet Radiol 25:210, 1984
59. Lombard CW, Spencer CP. Correlation of radiographic, echocardiographic and electrocardiographic signs of left heart enlargement in dogs with mitral regurgitation. Vet Radiol 26:89, 1985

8 Echocardiography and Doppler Imaging

N. SYDNEY MOÏSE
PHILIP R. FOX

Echocardiography plays an integral role in cardiovascular evaluation, providing accurate, noninvasive assessment of cardiac structure, function, and blood flow dynamics. Most importantly, echocardiography is a diagnostic test that should complement but not replace the survey thoracic radiograph. As such, it is of greatest value when guided by and incorporated into a complete data base.[1, 1a]

BASIC PRINCIPLES OF ULTRASOUND

Echocardiography is the clinical application of diagnostic ultrasound to examine the heart and proximal great vessels. Its diagnostic utility is enhanced by understanding basic physical principles.

GENERATION OF ULTRASOUND

Ultrasound is produced when a piezoelectric crystal housed in a transducer is electrically stimulated. The crystal expands and contracts to produce a series of sound waves. These are propagated in the form of a beam and transmitted into tissues. The greater the voltage applied to the crystal, the greater the transmitted pulse amplitude and intensity.[1, 2]

When emitted sound waves encounter an acoustic interface, they are reflected back to the transducer and produce electrical energy (sound waves are transmitted less than 1 percent of the time). The distance to the acoustic interface is calculated, since the speed of sound waves in soft tissues (average, 1540 m/sec)[2] and the time for the sound to travel are known. The echocardiograph computer processes all data to generate an image of acoustic interfaces. Image quality is determined by sophistication of the equipment, the proper match of transducer and structure, and the technical skills of the operator.

CHARACTERISTICS OF SOUND WAVES

Ultrasound travels through a medium as a propagating wave that causes the particles in the medium to oscillate. The amplitude and frequency of

displaced particles can be graphically expressed as a *sine wave*. The height above and below the baseline represents the degree of particle compression and rarefaction.[1] The *wavelength* of a given sound wave is determined by the distance between two similar points on the sine wave. The *frequency* of a sound wave represents the number of wavelengths that occur within a given time and is expressed in cycles/sec (cps) or hertz (Hz); 1 cps = 1 Hz. Frequency and wavelength are inversely related (e.g., the smaller the wavelength, the higher the frequency). The *velocity* of a sound wave in a medium equals the product of the frequency and wavelength, and it is primarily determined by density of the medium; denser structures increase sound wave velocity.[1, 3]

When sound waves meet a boundary between two different media, a portion of the acoustic energy is reflected, and part continues into the second medium. The ability to visualize structures with ultrasound is determined by the reflection of transmitted ultrasound. The *acoustic impedance* of a medium describes how sound travels through it. When a sound wave traverses the interface between two media that have different acoustic impedance properties, it is both reflected and refracted. Greater differences in acoustic impedance, termed *acoustic mismatch,* increase reflected and refracted sound waves.

Scattered echoes originate from irregular targets that are smaller than the wavelength of the ultrasound wave. They cause reflected echoes to be cast in many directions, resulting in only a few echoes being returned to the transducer.[1] Scattered echoes do not depend on the angle of incidence and are important in visualizing structures that are parallel to the ultrasound beam.

Specular echoes are reflected from large structures with smooth edges. They depend on the angle of the ultrasound beam to the tissue interface.

TRANSDUCERS AND THE ULTRASOUND BEAM

The ultrasound beam is relatively cylindric in shape as it leaves the transducer. The larger the radius and the smaller the wavelength (i.e., higher frequency), the farther the beam travels without divergence. Objects imaged within this *near field* will be visualized better than those outside this distance (*far field*). Higher-frequency transducers produce a more diagnostic near field. The amount of divergence can be electronically focused in some machines.

High-frequency transducers (i.e., 7.5 MHz) produce sound waves with a shorter wavelength, which allows reflection from smaller structures. This permits better structural definition and resolution but with less tissue penetration than lower-frequency transducers (e.g., 3.5 MHz).

Penetration of sound waves is influenced by the tissue.[1] Sound penetrates easier and travels straighter in homogeneous than in heterogeneous tissues. When more ultrasound is reflected, less is available for transmission through deeper tissues. Ultrasound travels in a straight line for a distance in the near field without diverging; it then diverges in the far field.[1]

ATTENUATION

Attenuation describes loss of ultrasound energy because of tissue absorption and sound wave scatter. The distance that ultrasound must travel to have half its energy attenuated is referred to as its *half-power distance* (cm)[3]; half-power distances include water, 380 cm; blood, 15 cm; soft tissue other than muscle, 1 to 5 cm; muscle, 0.6 to 1 cm; and lung, 0.05 cm (sound waves do not penetrate air). Thus, air is the "enemy" of ultrasound because of the great refraction and attenuation it causes; structures behind air cannot be adequately imaged. In contrast, effusions enhance imaging. Clearest images are obtained before removing pericardial or pleural fluid, although severe effusions may cause undue patient stress.

RESOLUTION

Resolution refers to the ability to distinguish between two small, separate objects or points. *Axial resolution* refers to the ability to resolve points lying along the path of the beam (i.e., one object behind the other) and is related to the wavelength, frequency, and duration of transmitted pulse. Resolution is approximately equivalent to twice the wavelength. For example, the wavelength of a 5 MHz transducer is 0.3 mm. Therefore, the resolution is approximately 0.6 mm. The lower the transducer frequency, the longer the wavelength and the poorer the resolution. *Lateral resolution,* the ability to differentiate points lying side by side relative to the ultrasound beam, is largely a function of beam width, which depends on transducer size, shape, frequency, and focusing. Structures parallel to the beam must be separated by more than twice the ultrasonic beam width to be resolved as laterally distinct.[1] *Azimuthal* (or elevational) *resolution* relates to the thickness of the imaging plane. Poor azimuthal resolution causes structural superimposition.

Object resolution is best if targets are situated centrally within a narrow ultrasound beam. Beam width can be changed by gain controls. If the gain is increased, the beam width increases, resolution decreases, and artifacts worsen.

TISSUE CHARACTERISTICS

When tissue does not reflect ultrasound, it is termed *anechoic* or *sonolucent.* If a tissue reflects ultrasound minimally compared with surrounding tissues, it is referred to as *hypoechoic.* Conversely, if a tissue is highly reflective, it is said to be *hyperechoic* (it has greater echogenicity). *Through-transmission* is a phenomenon in which ultrasound passes through a tissue that is anechoic or hypoechoic, and the next tissue to be struck with the ultrasound beam appears hyperechoic because of *acoustic enhancement* (e.g., greater echogenicity of the right ventricular wall is seen in animals with pericardial effusion). When an ultrasound beam strikes a calcified or dense object that blocks through-transmission, that object will be hyperechoic. However, the expected image behind it is usually absent, which is referred to as an *acoustic shadow.* Calcification is a common cause of acoustic shadowing.

TYPES OF ECHOCARDIOGRAPHY

Standard M-mode and two-dimensional (2-D) echocardiography evaluate cardiac chamber anatomy and motion. The best images result when structures are perpendicular to the ultrasound beam. Doppler echocardiography (spectral and color-flow) evaluates cardiovascular blood flow by assessing the relative change in returned ultrasound frequency compared with the transmitted frequency. Information is most accurate when Doppler sound waves are directed parallel to the target red blood cells (RBCs).[1, 3]

M-MODE ECHOCARDIOGRAPHY

M(motion)-mode echocardiography was the first widely used form of diagnostic cardiac ultrasound. Although 2-D echocardiography with its more intuitive image has largely replaced M-mode echo, the latter still has certain applications and value.[4]

ADVANTAGES. The sharp axial resolution and high sampling frequency of M-mode echo (1000 to 5000 pulses/sec) compared with the slower 2-D scanning rate (15 to 128 frames/sec) allow small, rapidly moving structures to be discerned and accurately correlated with time relative to the ECG. For example, M-mode echo is superior when resolving small cardiac dimensions or structures such as wall thicknesses in cats, in which 1 mm can make the difference between normal versus pathologic hypertrophy.

DISADVANTAGES. The limited image sector associated with a single, "icepick," one-dimensional beam focuses only on a very small portion of the heart (Fig. 8–1). This causes lack of consistent and accurate spatial orientation unless the M-mode is guided and derived from the 2-D image (i.e., the image is obtained and optimized with 2-D scanning, immediately followed by engaging the M-mode imaging format).

TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Two-dimensional echocardiography was developed to circumvent limitations associated with single beam M-mode interrogations.[1, 3]

ADVANTAGES. Utilizing an ultrasonic beam moving in a sector, 2-D echocardiography creates a pie- or fan-shaped image, displaying anatomic and functional characteristics that are more anatomically intuitive than M-mode imaging. Two types of commercial systems are available. (1) Mechanical scanners move the ultrasound beam by mechanically oscillating a single crystal rapidly within a prescribed arc, or by rotating multiple crystals on a spinning wheel within the transducer. These are relatively less expensive and produce better resolution under certain conditions, although they are often more bulky and are prone to higher maintenance needs. (2) Phased array scanners have multiple transducer elements arranged into thin crystals that are electronically fired in sequence without use of mechanical components. This produces a quieter, lighter transducer capable of dynamic focusing.

DISADVANTAGES. Compared with M-mode echocardiography, 2-D echo image acuity is less precise, and frame rate is slower. These factors are generally most important when precise measurements of small structures are contemplated.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

In contrast to standard transthoracic echocardiographic procedures in which the transducer is placed upon the chest surface, transesophageal echocardiography (TEE) uses a 2-D transducer at the end of a flexible endoscope placed in the esophagus to provide high-quality images. This results from closer proximity of the transducer to the heart. It is also possible to obtain Doppler information with this technique. Biplane or multiplane probes are preferred.[5–7]

Despite improved imaging, TEE has had limited veterinary application.[8, 9] Reasons include the high cost

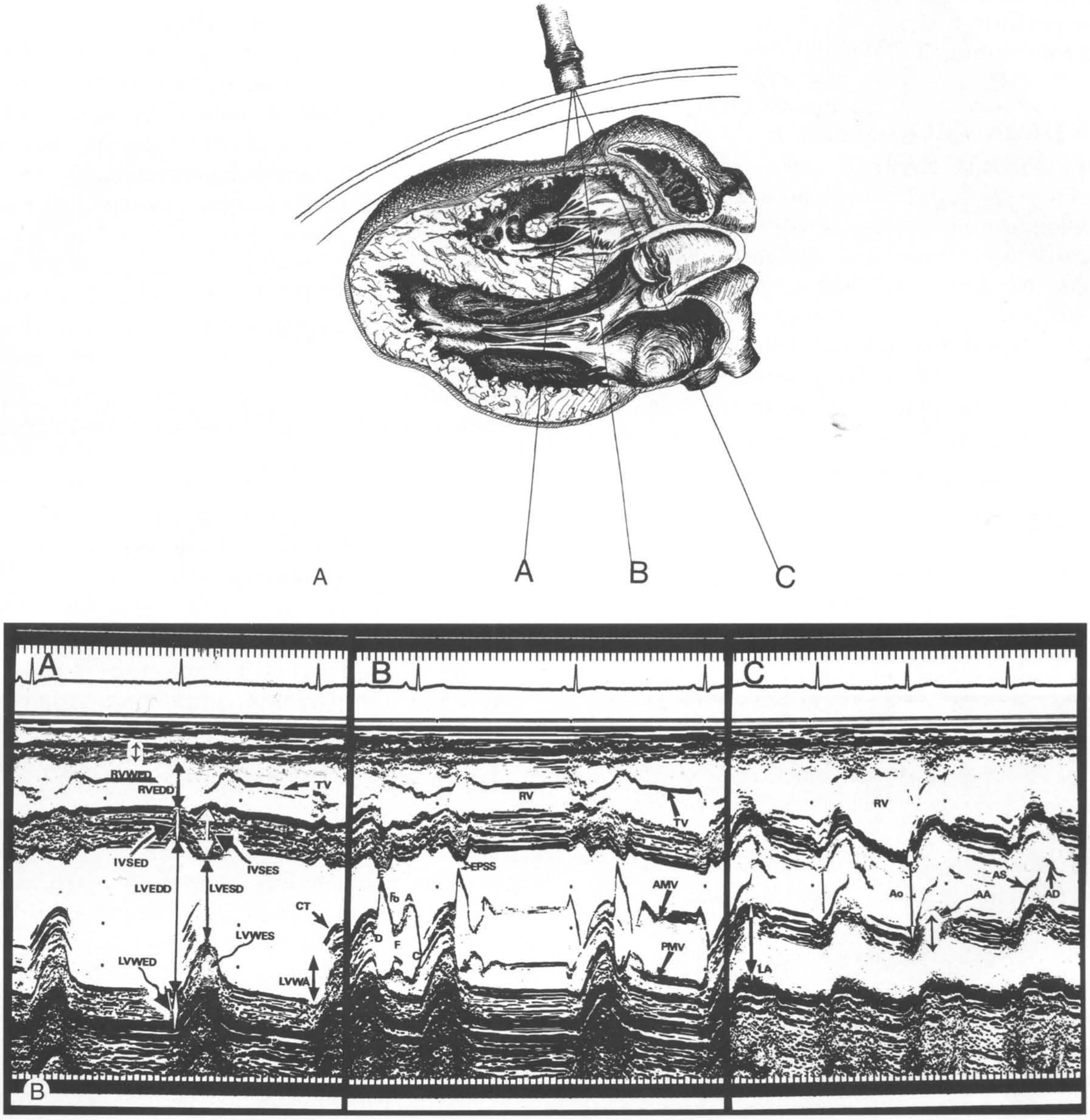


FIGURE 8–1

(A) Heart in long-axis view, depicting the three standard M-mode echo beam orientations. (B) Associated M-mode echo images of a normal dog. *Frame A* (apical left ventricular level at the level of the chordae tendineae): The transducer sends ultrasound waves (in sequence) through the right chest wall, right ventricular wall and chamber, interventricular septum, left ventricular chamber, chordae tendineae, and left ventricular free wall. *RVWED,* right ventricular wall at end-diastole; *RVEDD,* right ventricular end-diastolic diameter; *TV,* tricuspid valve; *IVSED,* interventricular septum at end-diastole; *IVSES,* interventricular septum at end-systole; *LVEDD,* left ventricular end-diastolic diameter; *LVESD,* left ventricular end-systolic diameter; *LVWED,* left ventricular wall at end-diastole; *LVWES,* left ventricular wall at end-systole; *LVWA,* left ventricular wall amplitude; *CT,* chordae tendineae.

Frame B (mid left ventricular, or mitral valve, level): The echo beam traverses the right heart. Depending on the transducer angle, it may intersect the tricuspid valve, the most basilar portion of the interventricular septum, the anterior and posterior mitral valve leaflets, and the left ventricular free wall. *RV,* right ventricle; *D,* initial mitral valve opening; *E,* maximum early diastolic mitral valve opening; *F,* closure of leaflets after early diastolic filling; the slope from E to F is the velocity of diastolic closure (and if this is not a straight line, point F_o is also used); *C,* closure of mitral leaflets just before systole; *EPSS,* E-point septal separation; *AMV,* anterior mitral valve; *PMV,* posterior mitral valve.

Frame C (aortic root and left atrial level): The echo beam traverses the right heart, aortic root and aortic valve, and left atrium. *RV,* right ventricle; *Ao,* aortic root; *AS,* aortic valve during systole; *AD,* aortic valve during diastole; *AA,* aortic amplitude; *LA,* left atrium. A simultaneous ECG is recorded to facilitate timing of the cardiac cycle.

of the specific transducers, the need to anesthetize the animal to perform this procedure, and increased time required for examination.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY

Technologic enhancements in 2-D imaging have fostered improved methodologies for assessing heart size and cardiac structure and function by three-dimensional echocardiography.[10, 10a] Advantages include the ability to assess anatomic geometry and associated ventricular function reliably; disadvantages include the need for special equipment, software, and training.

SPECIAL ECHOCARDIOGRAPHIC TECHNIQUES

In addition to transthoracic and transesophageal echocardiographic examination, other imaging techniques can sometimes provide useful information.[1a]

CONTRAST ECHOCARDIOGRAPHY

When Doppler echocardiography is unavailable, microbubbles in a peripheral venous injection reflect ultrasound and assist in identifying right-to-left intracardiac shunting. Microbubbles do not traverse the pulmonary or systemic capillaries but are filtered out by pulmonary capillaries with a diameter of 8 μ. They are easily created by agitating saline (3 to 10 ml) with 0.5 to 1 ml of air, or by a 1:4 mixture of the animal's blood and saline. Excess air is eliminated from the syringe and the agitated solution is immediately injected into a large vein during echocardiographic examination.

Simultaneous cardiac imaging visualizes blood flow by observing microbubbles entering the right atrium and right ventricle; if a right-to-left shunt is present, microbubbles appear in the left heart (Figs. 8–2, 8–3; see also Fig. 24–52*B*). A negative contrast effect is recorded by noncontrast-containing blood shunting into a chamber containing microbubbles (Fig. 8–3, *Frame 2*).

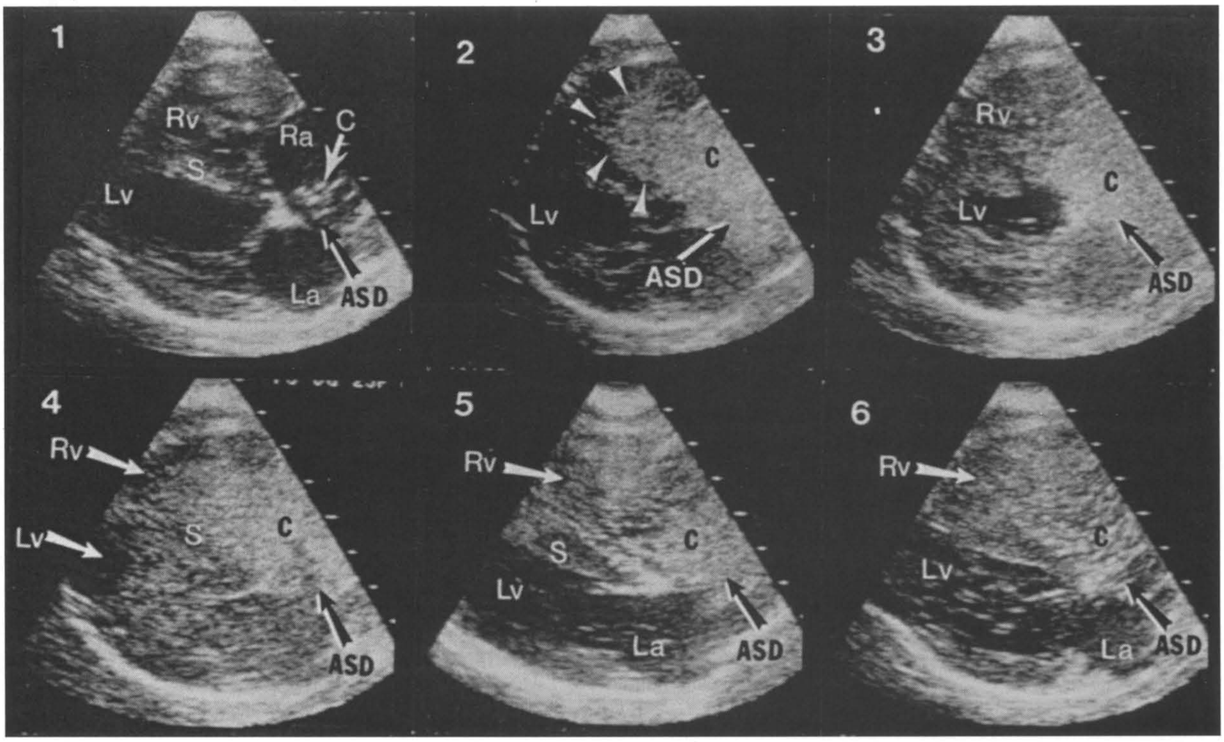


FIGURE 8–2

Contrast two-dimensional echoes (long axis four-chamber view recorded at the right parasternal position) of a boxer with an ostium secundum–type, predominantly right-to-left–shunting atrial septal defect. *Frame 1:* Contrast *(C)* first appears in the right atrium *(Ra)*. *Frame 2:* The contrast has filled the right atrium and right ventricle *(white arrows)* and has crossed the atrial septal defect *(ASD)* into the left atrium. *Frame 3:* The left atrium is filled with contrast. *Frame 4:* All chambers contain contrast. The echogenicity of the contrast bubbles is greater in the right heart. Contrast is still being injected and therefore continues to fill the right atrium. *Frame 5:* Contrast has virtually cleared from the left heart. *Frame 6:* Remaining contrast in the right heart continues to the atrial septal defect *(ASD)*, and bubbles are seen in the left ventricle. *Rv,* right ventricle; *S,* interventricular septum; *Lv,* left ventricle; *Ra,* right atrium; *La,* left atrium.

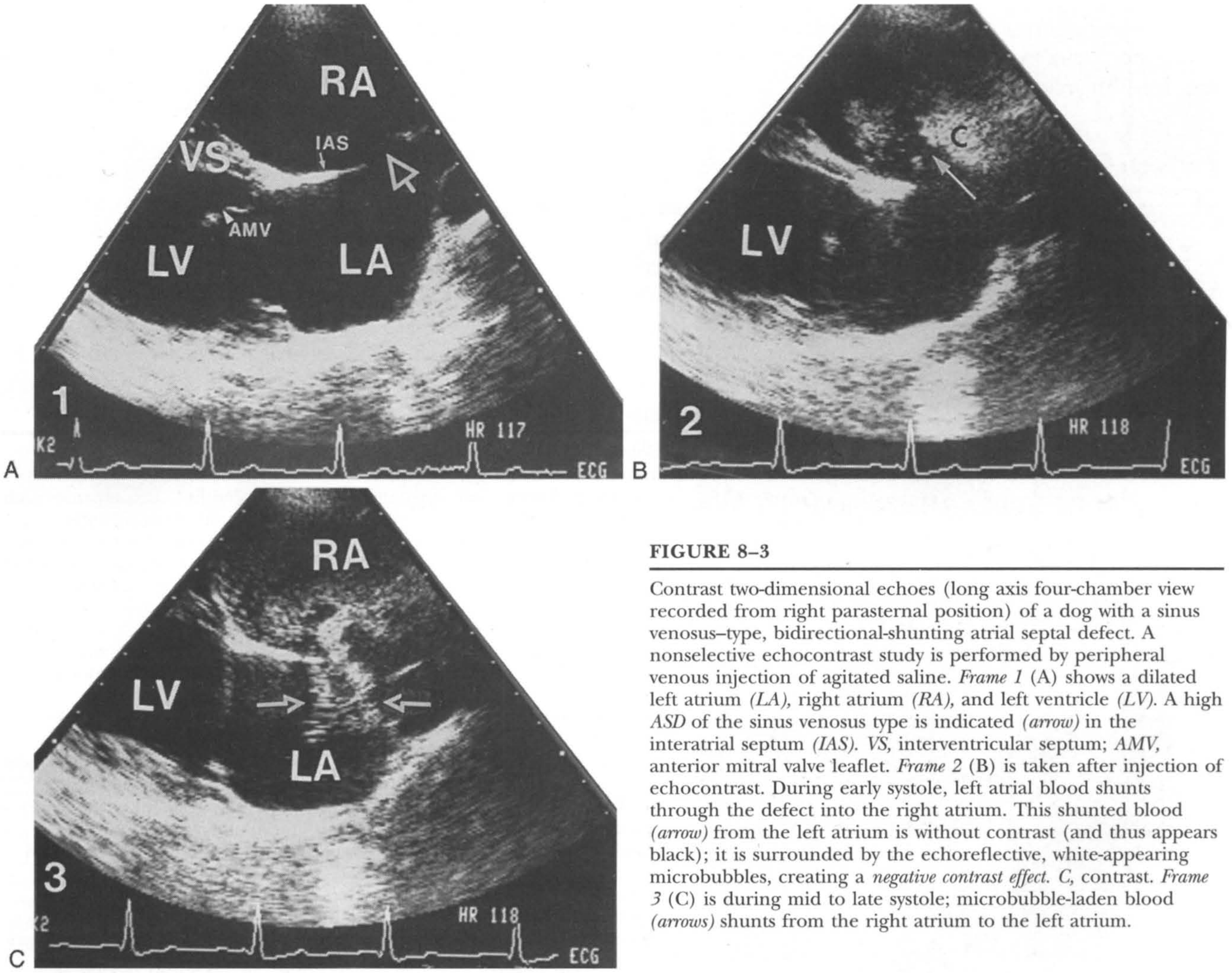


FIGURE 8–3

Contrast two-dimensional echoes (long axis four-chamber view recorded from right parasternal position) of a dog with a sinus venosus–type, bidirectional-shunting atrial septal defect. A nonselective echocontrast study is performed by peripheral venous injection of agitated saline. *Frame 1* (A) shows a dilated left atrium *(LA)*, right atrium *(RA)*, and left ventricle *(LV)*. A high *ASD* of the sinus venosus type is indicated *(arrow)* in the interatrial septum *(IAS)*. *VS*, interventricular septum; *AMV*, anterior mitral valve leaflet. *Frame 2* (B) is taken after injection of echocontrast. During early systole, left atrial blood shunts through the defect into the right atrium. This shunted blood *(arrow)* from the left atrium is without contrast (and thus appears black); it is surrounded by the echoreflective, white-appearing microbubbles, creating a *negative contrast effect*. *C*, contrast. *Frame 3* (C) is during mid to late systole; microbubble-laden blood *(arrows)* shunts from the right atrium to the left atrium.

DOPPLER ECHOCARDIOGRAPHY

Most cardiac disorders affect blood flow velocity or direction. Doppler echocardiography permits evaluation of these characteristics within the heart and great vessels. It utilizes the Doppler principle, which is based on the change in reflected sound wave frequency that occurs when sound waves strike a moving object.

Ultrasound waves generated from the transducer are reflected from red blood cells. Since the transmitted frequency is known and the frequency of reflected ultrasound is measured, the difference between transmitted and received signals can be determined. This shift in frequency, the *Doppler shift* or *Doppler frequency*, represents the difference in the transmitted and received frequencies.[11, 12]

Doppler echocardiography assesses direction and velocity of blood flow based upon measurement of the frequency shift of reflected ultrasound signals. Since *velocity = frequency × wavelength*, the magnitude of this shift is proportional to RBC velocity:

$$V = \frac{\Delta f \times C}{2f_o \times \cos \Theta}$$

where V is flow velocity of blood cells (m/sec); C is speed of ultrasound in blood; f_o is transmitted frequency (for any given transducer); Δf is shift in transmitted frequency (Doppler shift); and Θ is the intercept angle. By rearranging this equation

$$\Delta f = \frac{2f_o \times V \times \cos \Theta}{C}$$

TRANSDUCER FREQUENCY. According to these equations, the Doppler shift (Δf) is greatly influenced by transducer frequency. The higher the transducer frequency (e.g., 7.5 MHz versus 2.5 MHz), the lower the velocity of blood flow that can be measured.

DIRECTION OF BLOOD FLOW. Sound waves that strike RBCs moving toward the transducer are reflected off the RBCs at a higher frequency. This is displayed as a spectral recording above the baseline and denotes a positive Doppler shift (Figs. 8–4, 8–5; see also Figs. 8–15, 8–16*B*; 24–9*D*, 24–16, 24–38, and 24–56*D*). Conversely, sound waves that strike RBCs moving away from the transducer are reflected back at a lower fre-

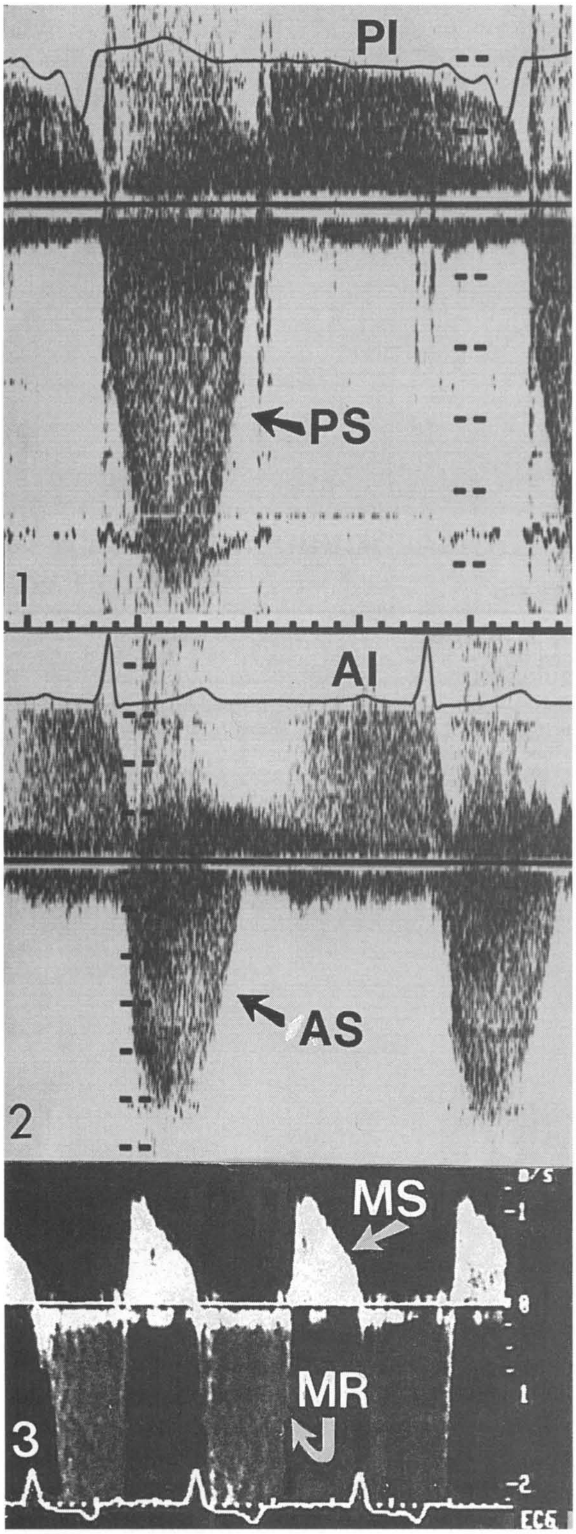


FIGURE 8–4

Continuous-wave Doppler echo examinations. A horizontal line in each frame indicates the baseline. In frames 1 and 2, the distance between markers = 1 meter/sec. A simultaneously recorded ECG accompanies each Doppler trace. *Frame 1:* Dog with congenital pulmonic stenosis; right cranial position with the Doppler courser placed through the RV outflow tract and pulmonary valves in the short-axis view. Blood flows during systole through the pulmonary valves away from the transducer (below the baseline), and the trace depicts increased velocity caused by pulmonic stenosis *(PS).* Using the modified Bernoulli equation ($\Delta P = 4 \times \text{velocity}^2$), the pressure gradient (ΔP) across the stenotic valves is approximately 121 mmHg [i.e., $4 \times (5.5 \text{ m/s})^2$]. There is also diastolic flow of pulmonic insufficiency (PI) toward the transducer (above the baseline).

Frame 2: Dog with congenital subaortic stenosis; left caudal (apical) position with the Doppler courser placed in the LV outflow tract in the five-chamber view. Blood flows during systole through the aortic valves away from the transducer, and the trace depicts increased velocity below the baseline from aortic stenosis *(AS).* The transvalvular gradient is about 110 mmHg [i.e., $4 \times (5.25 \text{ m/s})^2$]. There is also diastolic flow of aortic insufficiency (AI) toward the transducer (above the baseline) from blood regurgitating back through the aortic valves.

Frame 3: Cat with mitral stenosis; left caudal (apical) position with the Doppler courser placed through the mitral valves in the four-chamber view. Stenotic mitral valves increase peak transvalvular blood flow velocity in early diastole, followed by an abnormally slow diastolic descent. The mitral pressure half-time is greatly prolonged (80 to 100 msec; normal, less than 30 msec). *MS,* diastolic filling profile of mitral stenosis; *MR,* systolic jet of mitral regurgitation. ECG is at bottom.

quency. This is displayed as a spectral recording below the baseline and denotes a negative Doppler shift (Figs. 8–4, 8–5, 8–15, 8–16*F*; see also Figs. 24–1, 24–9*C*, 24–16, and 24–20).

ACCURACY OF DOPPLER VELOCITY DETERMINATION. The *intercept angle,* theta (Θ), is a key factor influencing the accuracy of gradients determined by Doppler echocardiography. It represents the angle between the ultrasound beam and the moving RBCs. When Doppler echo beam alignment is parallel to moving RBCs, blood velocity is most accurately measured. In contrast, 2-D and M-mode echocardiography require the beam to be perpendicular to tissue interfaces for ideal im-

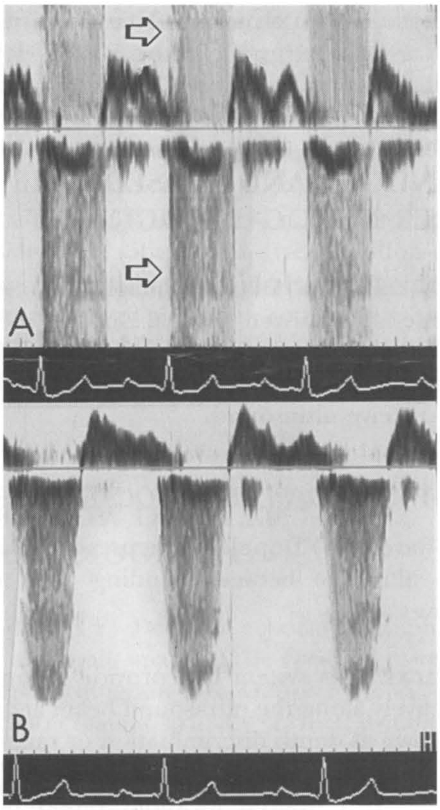


FIGURE 8–5

Pulsed-wave (A) and continuous (B) Doppler echo traces from a dog with chronic acquired mitral insufficiency imaged with a 3.25 MHz transducer. (A) The pulsed-wave Doppler sample gate was placed at the mitral valve orifice in the left apical four-chamber view. Peak diastolic transmitral filling velocities (1.5 m/s) appearing above the baseline are within the Nyquist limit (3.0 m/s) for this configuration and are accurately profiled. In contrast, the peak velocity of the systolic mitral regurgitation jet exceeds the Nyquist limit, and its spectral recording is aliased. This is depicted as a band "wrapping around" above and below the baseline *(arrows)*. (B) Continuous-wave Doppler echo differentiates both the direction and maximal velocity (approximately 5.6 m/s) of the systolic mitral regurgitant jet.

aging. When the Doppler beam is parallel to blood flow, the intercept angle between the ultrasound beam and blood flow is zero degrees, and *cos* Θ becomes 1. Measured velocity will then represent true velocity. If the intercept angle is wide, there will be a greater reduction in measured blood flow velocity compared with true velocity. Practically speaking, if the intercept angle is less than 20°, the percent error in velocity determination is less than 6 percent. Angles greater than 25° generally yield unacceptable quantitative estimates of velocity.

CHARACTERISTICS OF BLOOD FLOW

Blood flow velocities are represented as a spectral display or analysis of Doppler shift information. In reality, the spectral recording comprises a series of "bins" (vertical axis) recorded over time (horizontal axis), which represent the relative numbers of cells moving at a particular velocity. This velocity spectral analysis depicts a complex plot of the various velocities (Y axis) moving forward and backward in temporal association with the cardiac cycle.

DEFINITIONS. Cardiovascular blood flow has certain characteristics that can be measured with Doppler echocardiography. Normally, blood displays *laminar flow*. That is, most RBCs move with equal velocity, accelerate and decelerate in the same direction and at the same time, and have similar Doppler shifts. Normal blood flow through the heart and great vessels rarely exceeds 1.2 m/sec in the cat and 1.5 m/sec in the dog. Blood flow is pulsatile, exhibiting slightly different profiles with acceleration and deceleration.

Disturbed flow, or *turbulent flow*, results when there is disruption to the normal laminar pattern (e.g., by obstruction to flow). This causes the orderly movement of RBCs to become disorganized, resulting in whorls and eddies of different velocities and directions. Recorded Doppler shifts depict a profile of *spectral broadening* caused by heterogeneity of blood flow direction and velocities.

PATHOLOGIC VERSUS NONPATHOLOGIC TURBULENT FLOW. Turbulent flow patterns can exist without structural cardiac abnormalities when flow velocities are increased, or with congenital or acquired conditions.[1] Transition of laminar to turbulent flow occurs over a wide range of flow rates. This has been estimated by the *Reynold's number*, a dimensionless parameter used to characterize flow. As it increases, so does the tendency toward turbulent flow. The Reynold's number (Nr) is represented by the equation

$$Nr = (2r)(v)\ (p/\eta)$$

where *r* is the radius of the cylinder, *v* is the mean flow velocity, *p* is the mass density of blood, and η is the blood viscosity. Within pipes, the tendency for turbulent flow increases as the Reynold's number approximates a value of 2300. Thus, turbulent flow patterns can occur in some normal animals with rapid blood flow in large vessels. This is most often encountered in practice during clinical evaluation of a soft, systolic murmur, especially in young, large-breed dogs immediately following exercise, when rapid flow through the proximal aorta may occur. Thus, in dogs with "innocent" or "functional" murmurs, 2-D examination will reveal normal cardiac structure and function, and Doppler echo studies disclose relatively normal flow dynamics, except for slightly increased transvalvular velocity.

In contrast, flow through a small (stenotic) orifice into a larger chamber causes turbulence at a lower Reynold's number (200 to 500). For example, a small,

left-to-right–shunting ventricular septal defect (VSD) has reduced radius (r) with increased driving pressure from the left ventricle. This causes much turbulence (and a loud murmur) but an insignificant shunt volume. Alternatively, severe mitral regurgitation with mitral valve dysplasia may cause minimal turbulence (and a soft murmur) but a significant regurgitant volume. This results from a very large valve orifice (radius) and huge receiving chamber, which lower the turbulent threshold.

DERIVED INFORMATION FROM DOPPLER EXAMINATION

Using velocity data obtained from the Doppler examination and dimensional information obtained from the echocardiographic image, a variety of calculations can be made. These include intracardiac chamber pressures,[12–15] pressure gradients,[12, 16–19] flow volume and output,[20–25] valve area,[26–28] regurgitant fractions,[20] shunt ratios,[24, 25] and others. Interrogation of cardiac blood flow by Doppler echocardiography can provide extensive information relative to the presence, location, and extent of abnormal flow, obstruction to blood flow, and systolic or diastolic dysfunction.

ESTIMATION OF PRESSURE GRADIENTS. Obstruction to blood flow (e.g., valvular stenosis) increases velocity across the stenotic region. Resultant systolic jets may attain maximal peak velocities of 5 or 6 m/sec. The gradient (i.e., pressure drop) across an obstruction may be calculated by the simplified *Bernoulli equation*:

$$p_1 - p_2 \cong 4v^2$$

where $p_1 - p_2$ approximates the pressure gradient across an obstruction (e.g., across a stenotic valve), and v is the maximal velocity distal to the obstruction (see Fig. 8–4).

Differences exist between pressure gradients calculated by Doppler studies and cardiac catheterization (Fig. 24–1). Doppler studies are usually performed in unanesthetized patients and represent the *maximal* (peak) *instantaneous pressure gradient*. Doppler echocardiography may underestimate maximal blood flow velocities and calculated pressure gradients if parallel beam orientation to blood flow is not attained. The Doppler echo peak instantaneous gradients are usually higher than the catheterization-derived peak-to-peak gradients.[17] In contrast, commonly reported catheterization-derived gradients represent the ventricular to systemic artery *peak-to-peak pressure gradient*. Measurement of the peak instantaneous catheterization gradient is usually higher than the peak-to-peak gradient, but accurate measurement of the former requires more time and is prone to error, especially when fluid-filled catheters are used. Cardiac catheterization requires anesthesia, which may reduce ventricular pressures and associated gradients by 50 to 60 percent, compared with most Doppler echo examinations.

CONTINUOUS AND PULSED-WAVE DOPPLER ECHOCARDIOGRAPHY

Prior to color-flow Doppler imaging, conventional Doppler methods utilized spectral Doppler techniques in the form of continuous and pulsed-wave Doppler echocardiography. Each uses the same transducer to send and receive ultrasound.

PULSED-WAVE DOPPLER ECHOCARDIOGRAPHY

Pulsed-wave (PW) Doppler echo uses the same transducer to alternate between sending and receiving sound waves.

ADVANTAGES. This system can provide Doppler shift data selectively along the ultrasound beam at any given range (known as depth discrimination or range resolution) by positioning an electronically controlled sample volume to a desired location. Blood flow at a specific point within the heart or vessel can be measured by adjusting the time-gate delay control to receive only the ultrasound waves reflected from RBCs at that particular point and depth. Blood flow can be "mapped" as to the location, extent, and velocity of abnormal flow by manually and systematically moving the sample gate within a vessel or cardiac chamber. This time-consuming process is shortened with color-flow Doppler echocardiography (discussed later).

DISADVANTAGES. Pulsed-wave Doppler echocardiography has limited ability to measure high blood flow velocities such as occur frequently with acquired or congenital valvular diseases. To measure blood flow velocity accurately, the sampling rate must be sufficiently high relative to the flow velocity of interest (see Nyquist limit, later). Also, since beam divergence occurs, the farther into the heart the sample volume is placed, the larger it becomes, and depth resolution becomes compromised.

CONTINUOUS-WAVE DOPPLER ECHOCARDIOGRAPHY

Continuous-wave (CW) Doppler echocardiography uses separate transmitting and receiving crystals within a transducer. This enables ultrasound waves to be continuously transmitted and received.

ADVANTAGES. CW Doppler echocardiography accurately measures high blood velocities. In certain con-

genital disorders, it is important to evaluate maximal blood flow velocities and quantitatively evaluate true blood flow profiles. This is most important when assessing the severity of gradients caused by aortic and pulmonic valvular stenosis.

DISADVANTAGES. CW Doppler echocardiography is unable to selectively sample at a given location and lacks depth discrimination. The CW beam contains Doppler shift information all along the course of its ultrasound beam. It does not allow selective placement of a given Doppler sample volume, making it difficult to localize defects.

COLOR-FLOW DOPPLER ECHOCARDIOGRAPHY

Color-flow (CF) Doppler echocardiography synthesizes the anatomic image of the two-dimensional or M-mode echocardiogram with Doppler blood flow characteristics to create a spatially correct, dynamic image. Color-flow mapping speeds the complete Doppler echocardiographic examination.[29–32]

Because CF Doppler echoes are derived from pulsed-wave Doppler echocardiography, they are subject to similar limitations. In contrast to pulsed-wave Doppler, which has a single-range gate or sample volume, CF Doppler utilizes multiple sampling gates to construct a composite image.[31] This is accomplished by sampling every point in the scan plane (*line density*) to determine the Doppler shift from the returning signals and processing these data when the multiple gates are analyzed.

Increased spatial information of blood flow is achieved when ultrasound waves are emitted as bursts of pulses, called a *pulse train*.[32] The *pulse repetition frequency* (PRF) is determined by the time between pulse trains. The *packet size* describes a burst of ultrasound pulses, which is determined by successive pulse trains along a given line at a given angle. The higher the packet size and the greater the line density, the better the color image. However, the larger the packet size, the smaller the line density, and vice versa. Line density and packet size are automatically adjusted when the echocardiographer selects the sector angle and depth range. Color images are maximized by the narrowest sector angle and low imaging depth, but these settings decrease spatial orientation. Thus, trade-offs exist between instrumentation settings for obtaining the best image. These are manipulated by the operator to achieve the optimal desired format for particular needs.

The mean frequency-shift obtained from the multiple gates or sample volumes is coded with color to indicate direction and velocity.[31–33] By standard convention, blood flowing toward the transducer is coded red, and blood flowing away from the transducer is coded blue. Blood flow velocity is indicated by the intensity of the color. Thus, slowly moving blood is colored dark; faster-moving blood is colored brightly.

VARIANCE

When blood flow is laminar, mean velocity is close to peak velocity. In contrast, turbulent flow causes broadening of the velocity spectrum, with many different velocities occurring simultaneously. Variance expresses the degree that velocities within a given sample volume differ from the mean velocity. Echocardiographs incorporate methods to detect this spectral broadening variance detection by use of color-enhanced variance maps. These add shades of green or vary hues of blues and reds with brighter and less bright colors to detect variance.[32]

ALIASING AND THE NYQUIST LIMIT

When blood velocity exceeds the ability of pulsed-wave Doppler to record it accurately, the phenomenon of *aliasing* occurs. The *Nyquist limit* defines the maximal velocity that can be recorded by pulsed-wave Doppler without aliasing:

$$\text{Nyquist limit} = \frac{\text{Number pulses/sec}}{2}$$

This specifies that measurements of frequency shifts (i.e., blood velocity) are accurate only when the pulse repetition frequency (PRF) is at least twice the detected maximal velocity (i.e., the Doppler shift frequency).[1]

Aliasing is depicted on the spectral display as a band that "wraps around" the baseline and results in ambiguous depiction of the velocity profile (see Fig. 8–5*A*). Because color-flow Doppler is a form of pulsed-wave Doppler, determination of high-velocity blood flow is subject to the same limitations. Aliasing is manifested by the colors "wrapping around" and results in color reversal. For example, if the velocity of blood flow moving toward the transducer exceeds the Nyquist limit, the normal red color will become very bright or light orange; it will turn to very light blue or white when higher velocity is detected; and ultimately, it turns to darker shades of blue if velocities are higher yet.

CONTROL OF ALIASING AND THE NYQUIST LIMIT

The Nyquist limit (i.e., the maximal recordable velocity with PW Doppler) is controlled by two factors: (1) depth into the tissue, and (2) transducer frequency. The maximum PRF is limited by the distance

into the heart that the sample volume is placed. The closer the sample volume is located to the transducer, the higher the maximum PRF (and the higher the Nyquist limit). Conversely, the farther the sample volume is placed into the heart, the lower the maximal PRF becomes, and in a practical sense, the lower the maximal velocity that can be recorded without aliasing.

Transducer frequency affects the Nyquist limit (i.e., the maximal recordable velocity with PW Doppler). Switching to a lower-frequency transducer increases the maximal velocity that can be recorded until the Nyquist limit is exceeded. The disadvantage of a low-frequency transducer is that it reduces the signal-to-noise ratio and related image quality. Another technique to overcome signal aliasing is to move the baseline to the top or bottom of the trace, which expands the frequency range.

THE TWO-DIMENSIONAL AND M-MODE ECHOCARDIOGRAPHIC EXAMINATION

The foundation of diagnostic echocardiography is two-dimensional imaging. Therefore, selection of a machine that provides high image quality is critical. The greatest usefulness of Doppler echocardiography is for congenital heart disease evaluation, although assessment of certain acquired disorders is often assisted.

To provide maximal diagnostic information, the echocardiographic examination should systematically evaluate multiple tomographic planes from both sides of the thorax, beginning with 2-D echocardiography, and followed by M-mode, color-flow mapping, and spectral Doppler echocardiographic techniques.[34, 35] This requires that the clinician (1) understand normal three-dimensional cardiovascular anatomy and relate it to images obtained from various imaging planes, (2) recognize and understand the effects of pathologic changes on cardiac structure and function, and (3) apply the basic principles of diagnostic ultrasound to adjust the instrument, maximizing diagnostic image quality.

Although most animals do not require tranquilization, some cases require chemical restraint to facilitate a good examination. Chemical agents variably alter heart rate, indices of cardiac function, and Doppler measurements.

Transthoracic imaging does not usually require shaving the hair. However, generous application of coupling gel is always beneficial.

Appropriate patient positioning facilitates transthoracic echocardiographic examinations. An elevated platform (wood or Plexiglas) with cut-out holes, or a table with cut-out holes or notches upon which the patient is placed (Fig. 8–6) is very helpful. With the animal restrained in lateral recumbency over the appropriate-sized hole, the transducer is directed up through the hole against the thorax. This allows the heart to lie closer to the dependent thoracic wall and thus, nearer the transducer.

Selection of a transducer with optimal frequency for the individual is important; echocardiographic instruments and patient size must be considered. In general, high-frequency transducers (e.g., 7.5 MHz) provide the best 2-D and M-mode image detail but have less tissue penetrating ability and are unable to record high-velocity blood flow in the Doppler mode. The latter is facilitated by lower-frequency transducers.

Examinations usually start from the right parasternal position. Once the heart is visualized, the depth setting is optimized, followed by the time gain compensation (TGC) controls (adjusted to compensate for loss of ultrasonic energy as the beam traverses the thorax), and the degree of reject and compression is set. With color-flow mapping, adjustments in frame rate, quality, sector angle, and other manipulations are made to optimize structures of interest in each view.

The transducer is initially positioned in the right 4th to 5th intercostal space. In directing the transducer, it is important to remember that the long- and short-axis views refer to the heart and not to the thorax. It may be helpful to conceptualize the heart as it appears in

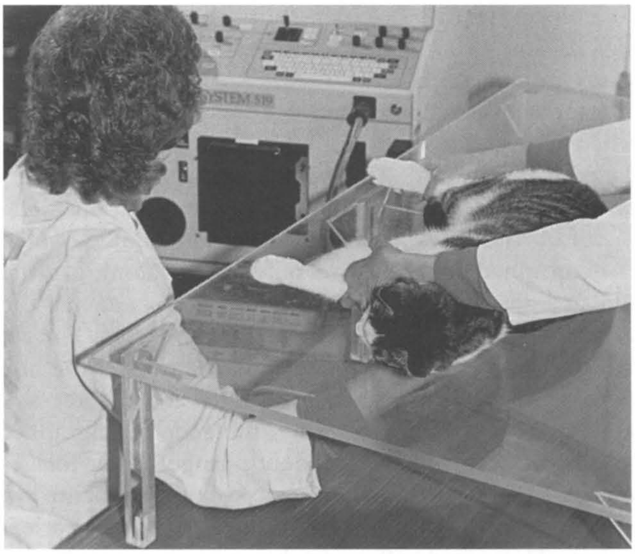


FIGURE 8–6

Patient examination table that we use for transthoracic echo and Doppler echo examination. Rectangular or circular holes are cut into the platform. The patient is restrained in lateral recumbency with the desired thoracic location ("window") placed over the appropriately sized hole. The transducer is then introduced from the bottom. When a rectangular opening is used, smaller animals can be positioned at an angle and larger animals along its long axis to obtain the best access.

thoracic radiographs during the examination. Standard echocardiographic views are then obtained.[35–40]

STANDARD IMAGING PLANES FOR TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Standard imaging planes (also called views) have been adapted from human echocardiography and modified for animals (Fig. 8–7).[35, 36] They are designated based upon (1) transducer location (also called "windows"), (2) spatial orientation of the imaging plane, and (3) recorded structures. For example, "right parasternal long axis" describes a view recorded with the transducer positioned on the right parasternal location and the imaging plane oriented parallel to the left ventricular long axis. Animals vary with respect to optimal transducer locations.[36]

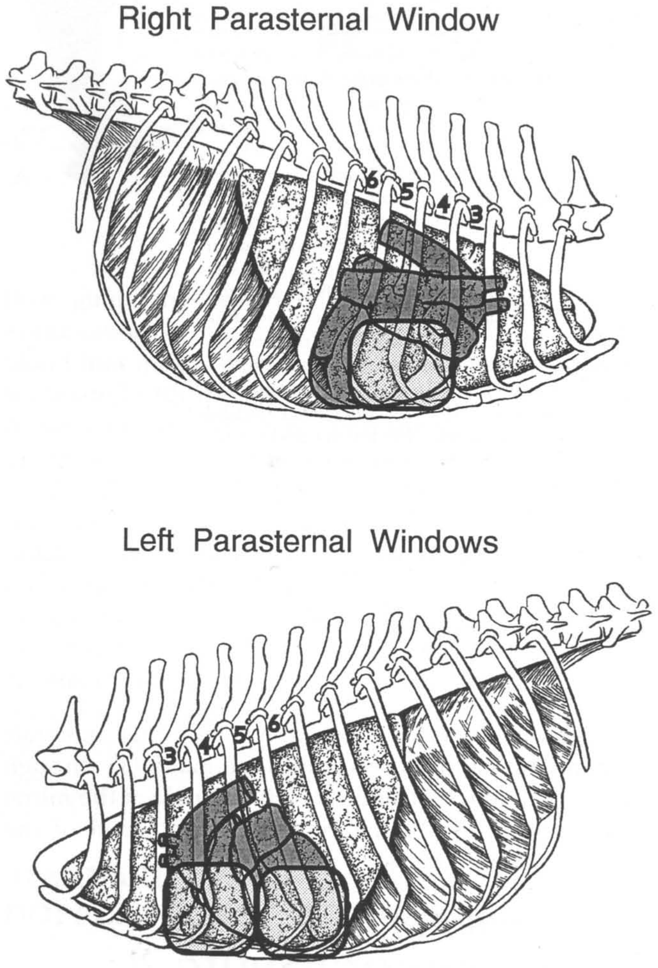


FIGURE 8–7

Standard transducer locations ("windows") for transthoracic echocardiography. See text for details. (From Thomas WP, Gaber CE, Jacobs J, et al. Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. J Vet Intern Med 7:247–252, 1993, with permission.)

RIGHT PARASTERNAL LOCATION

This transducer location is between the right 3rd and 6th (usually 4th to 5th) intercostal spaces (Fig. 8–7). The two principal imaging planes include long-axis views (Fig. 8–7*A*) and short-axis views (Fig. 8–7*B*). The M-mode echocardiogram is usually derived from either the long-axis view showing part of the left atrium and aorta, or the short-axis views. When recording the M-mode from short-axis views, it is important to transect the heart directly in the middle in the true minor axis and avoid angled or oblique views.

LONG-AXIS VIEWS. Two views are generally obtained (Fig. 8–8*A*): (1) a four-chamber view with the ventricles (cardiac apex) displayed to the left and atria (cardiac base) displayed to the right, and (2) a second view obtained by slight clockwise transducer rotation showing the left ventricular (LV) outflow tract, aortic valve, and aortic root.

SHORT-AXIS VIEWS. These are obtained by rotating the transducer and beam plane 90° from long-axis views (Fig. 8–8*B*). By then angling the beam plane from apex (ventral) to base (dorsal), a series of progressive views are obtained at the level of the LV apex, papillary muscles, chordae tendineae, mitral valve, and aortic valve, respectively.

LEFT CRANIAL PARASTERNAL LOCATION

This is located between the left 3rd and 4th intercostal spaces between the sternum and costochondral junctions (Fig. 8–9*A*).

LONG-AXIS VIEWS. A series of views may be obtained with the beam plane oriented approximately parallel with the long axis of the body and heart (Fig. 8–9*A*).

SHORT-AXIS VIEWS. A series of short axis orientations is obtained by rotating the transducer beam 90° from the long-axis view (Fig. 8–9*B*).

LEFT CAUDAL (APICAL) LOCATION

This location is close to the sternum between the 5th and 7th intercostal spaces (Fig. 8–10).

LEFT APICAL FOUR- AND FIVE-CHAMBER VIEWS. A four-chamber view of the heart oriented vertically may be obtained with the left side of the heart appearing to the right, the right side of the heart appearing to the left, and the ventricles in the near field (Fig. 8–10*A*). A left ventricular outflow region may be brought into view by tilting the beam slightly cranial from the four-chamber view. A five-chamber view is denoted when all four cardiac chambers, both atrioventricular valves, and the aortic valve appear in one plane.

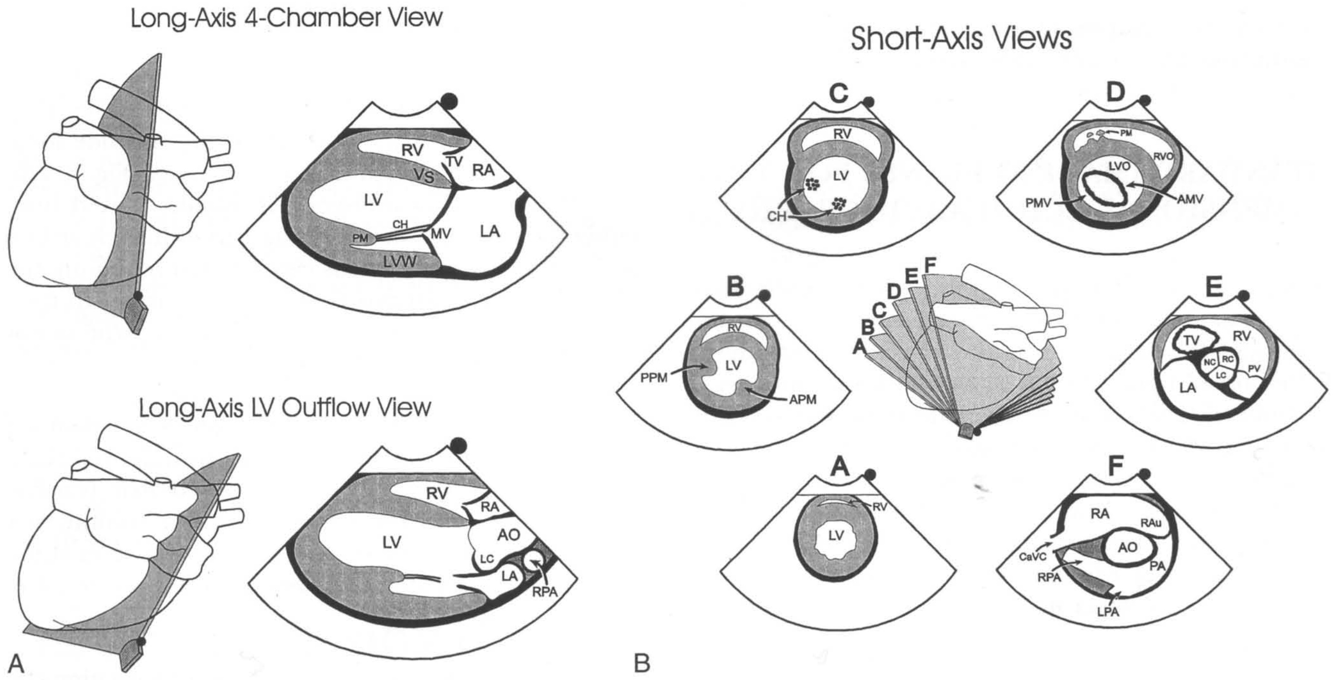


FIGURE 8–8

Two-dimensional echo views recorded from the right parasternal transducer location. Illustrations of the heart displayed from the right side contain different echo transducer alignments. These fan-shaped echo beam orientations transect the heart to produce corresponding tomographic 2-D echo images.

(A) Long-axis four-chamber view and long-axis view that optimizes the left ventricular outflow region. In the long-axis view that optimizes the LV outflow region, the body of the left atrium, left ventricle, and aorta usually cannot be imaged together in a single plane from this location. This results in only a small portion of the left atrium being imaged, compared with the four-chamber view. *RV,* right ventricle; *TV,* tricuspid valve; *RA,* right atrium; *LV,* left ventricle; *VS,* interventricular septum; *LVW,* left ventricular posterior (caudal) wall; *CH,* chordae tendineae; *PM,* papillary muscle; *MV,* mitral valve; *LA,* left atrium; *AO,* aorta; *LC,* left cusp (aortic valve); *RPA,* right pulmonary artery. (B) Two-dimensional short-axis echo views obtained from the right parasternal transducer location. The center diagram illustrates the beam orientations used to obtain images at six levels of the left ventricle. Corresponding images are depicted clockwise starting from the bottom. Sections *A* to *F* show progressive views from the level of the apex *(A),* papillary muscle level *(B),* chordae tendineae level *(C),* mitral valve level with the mitral valves open during diastole *(D),* aortic valve level (diastole) *(E),* and basilar level showing the pulmonary arteries *(F). RV,* right ventricle; *LV,* left ventricle; *CH,* chordae tendineae; *PM,* papillary muscle; *LVO,* left ventricular outflow tract; *PMV,* posterior (parietal) mitral valve cusp; *RVO,* right ventricular outflow tract; *AMV,* anterior (septal) mitral valve cusp; *PPM,* posteromedial (dorsal) papillary muscle; *APM,* anterolateral (ventral) papillary muscle; *PV,* pulmonary valve; *RA,* right atrium; *TV,* tricuspid valve; *LA,* left atrium; *NC,* noncoronary or septal aortic valve cusp; *RC,* right aortic valve cusp; *LC,* left aortic valve cusp; *CaVC,* caudal vena cava; *PA,* main pulmonary artery; *RPA,* right pulmonary artery; *LPA,* left pulmonary artery; *RAu,* right auricle; *AO,* aorta. (From Thomas WP, Gaber CE, Jacobs J, et al. Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. J Vet Intern Med 7:247–252, 1993, with permission.)

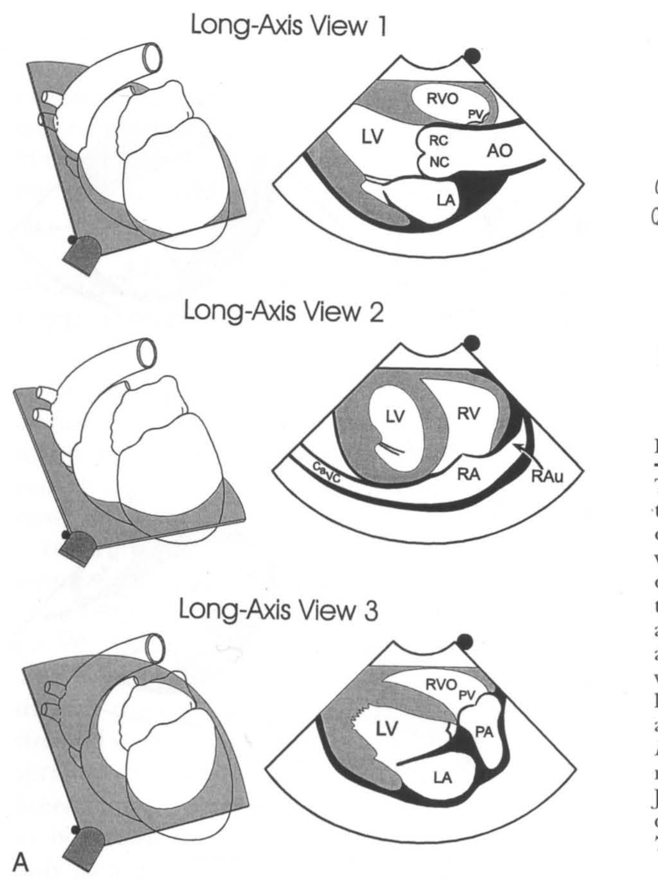
LEFT APICAL TWO-CHAMBER VIEWS. When the beam plane is nearly perpendicular to the long axis of the body and parallel to the long axis of the heart, a two-chamber long-axis view is obtained of the left atrium, mitral valve, and left ventricle (Fig. 8–10*B*).

STANDARD IMAGING PLANES FOR M-MODE ECHOCARDIOGRAPHY

M-mode echocardiograms are derived from 2-D images that guide proper spatial and anatomic orientation. Most M-mode data are derived from the right parasternal long-axis view of the left ventricle, although the short-axis views often allow better anatomic alignment. Standard recordings are made (1) through the aorta and left atrium, (2) left ventricle at the mitral valve level, and (3) left ventricle at the level of the chordae tendineae (see Fig. 8–1).

THE DOPPLER ECHOCARDIOGRAPHIC EXAMINATION

If color-flow Doppler echocardiography is available, it is used first to map abnormal flow patterns and



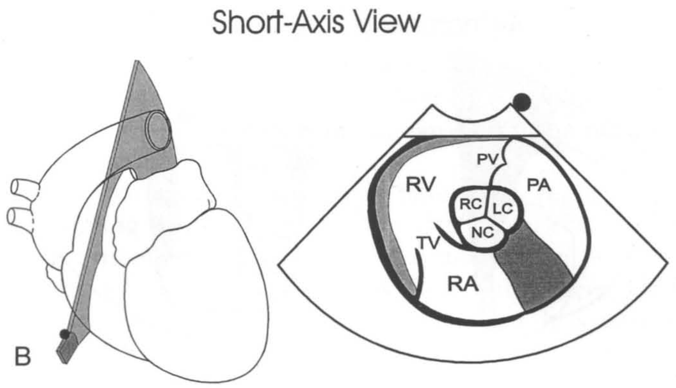


FIGURE 8–9

Two-dimensional echo views obtained from the left cranial parasternal transducer location. (A) Long-axis views: *View 1* accentuates the LV outflow region. *View 2* is an oblique view showing the left and right ventricle, tricuspid valve, right atrium inflow region, and long-axis view of the right atrium and caudal vena cava. *View 3* shows the RV outflow tract, pulmonary valve, and main pulmonary artery. (B) *Short-axis view* at the level of the aortic root. Note that the right ventricular inflow and outflow tracts are displayed. For (A) and (B): *RVO,* right ventricular outflow tract; *PV,* pulmonary valve; *TV,* tricuspid valve; *LV,* left ventricle; *RC,* right aortic valve cusp; *NC,* noncoronary or septal aortic valve cusp; *LC,* left aortic valve cusp; *AO,* aorta; *LA,* left atrium; *PA,* pulmonary artery; *RV,* right ventricle; *CaVC,* caudal vena cava; *RA,* right atrium; *RAu,* right auricle. (From Thomas WP, Gaber CE, Jacobs J, et al. Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. J Vet Intern Med 7:247–252, 1993, with permission.)

then guide the pulsed or continuous-wave Doppler examination in order to attain maximal velocity for blood flow measurements.[41] The Doppler examination is initiated with the animal positioned in right lateral recumbency (see Fig. 8–8). The animal is then turned to left lateral recumbency and examined both from a cranial (Fig. 8–9) and caudal (apical) (Fig. 8–10) position. For optimal Doppler studies, the ultrasound beam is directed as parallel as possible to blood flow. From the cranial position, the base of the heart and the great vessels can be thoroughly interrogated. From the caudal (apical) position, the two-chamber, four-chamber, and five-chamber views of the heart can be seen. Each cardiac transection offers a different anatomic perspective.

STANDARD IMAGING PLANES FOR DOPPLER ECHOCARDIOGRAPHY

Transducer locations and imaging planes described for 2-D imaging are used for Doppler echocardiographic studies. Views that provide optimal parallel beam orientation are selected. Two additional locations may be useful.

SUBCOSTAL LOCATION

With the animal in right or left lateral recumbency, the transducer is placed under the xiphoid and pushed dorsally into the abdomen, while held roughly parallel to the vertebral column. An apical two-chamber view, including the descending aorta oriented parallel to the transducer beam, can be obtained. Some animals object to this abdominal pressure unless sedated.

SUPRASTERNAL LOCATION

Although uncommonly used in veterinary medicine, this location may provide good alignment between aortic blood flow and the Doppler echo beam. The transducer is placed in the thoracic inlet and the beam directed toward the ascending aorta.

GENERAL PRINCIPLES OF ECHOCARDIOGRAPHIC MEASUREMENT

Cardiac dimensions have been assessed from either the M-mode or the 2-D echocardiogram.[37, 38, 42, 43] Dimensional measurements are more accurate when calculated from 2-D echo-guided M-mode traces. A variety of derived left ventricular calculations can be made

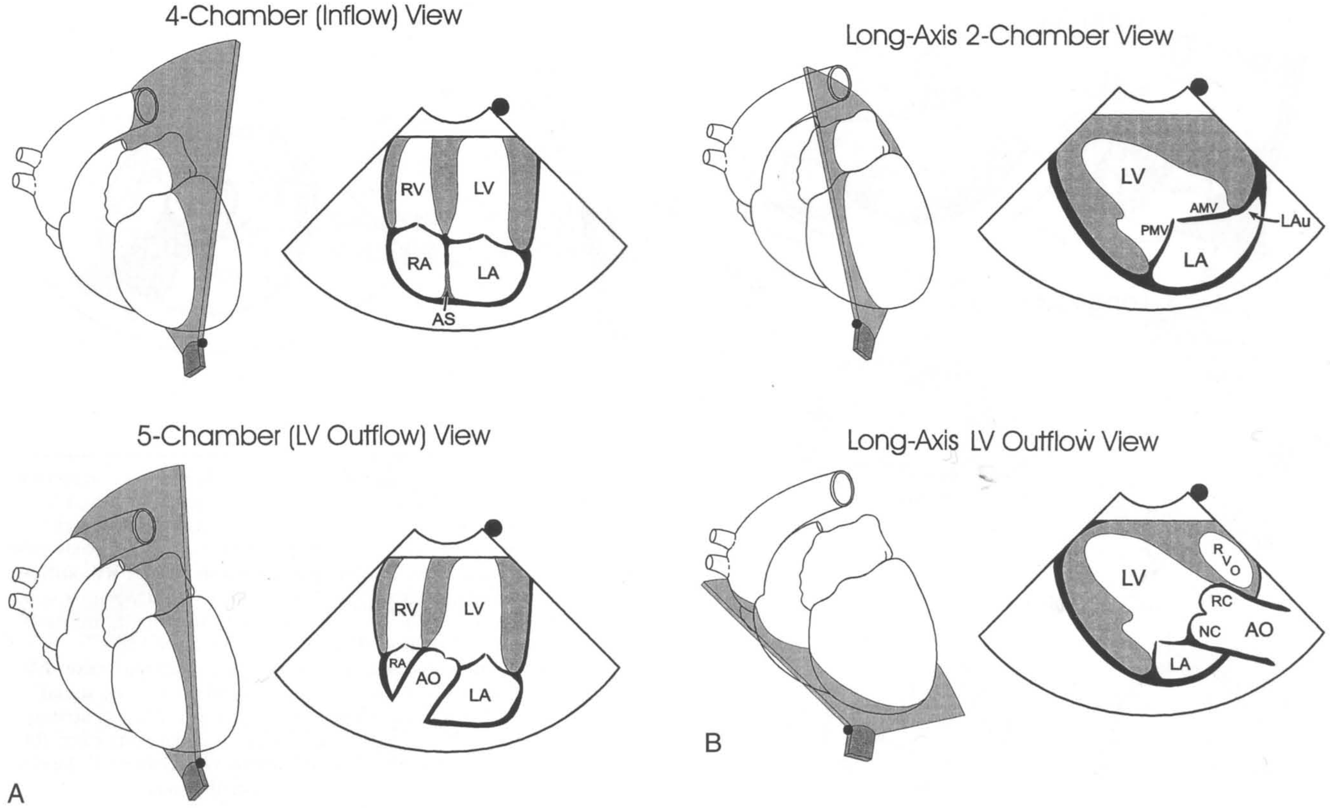


FIGURE 8–10

Two-dimensional echo views obtained from the left caudal (apical) parasternal transducer location. (A) Four-chamber inflow view displays all four cardiac chambers and provides optimal alignment for Doppler echo studies of mitral and tricuspid inflow. Slight cranial tilting of the beam produces the five-chamber view showing the LV outflow tract in addition to the left and right ventricular inflow tracts. (B) The long-axis two-chamber view and LV outflow view are obtained by directing the beam plane nearly parallel to the long axis of the heart. *RV,* right ventricle; *LV,* left ventricle; *LA,* left atrium; *LAu,* left auricle; *VS,* ventricular septum; *AS,* atrial septum; *RA,* right atrium; *RVO,* right ventricular outflow tract; *AO,* aorta; *AMV,* anterior (septal) mitral valve cusp; *PMV,* posterior (septal) mitral valve cusp; *NC,* noncoronary or septal aortic valve cusp; *RC,* right aortic valve cusp. (From Thomas WP, Gaber CE, Jacobs J, et al. Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. J Vet Intern Med 7:247–252, 1993, with permission.)

from measurements of cardiac dimensions, including volume, LV mass, and wall stress.

MEASURING TECHNIQUES

Different methods have been described for measuring M-mode and 2-D images. Although variations are reported,[4] the most widely accepted standards follow recommendations set by the American Society of Echocardiography,[42] using the *leading edge method* for measuring. The leading edge represents the part of the line closest to the transducer; the trailing edge is the part of the line farthest from the transducer. Dimensions and wall thicknesses are measured from leading edge to leading edge.

Measurements are timed to specific reference points in the cardiac cycle, according to simultaneous ECG recording (see Fig. 8–1). The higher M-mode sampling rate allows more precise timing and resolution than 2-D echocardiography. *End-diastole* is most reliably measured at the onset of the QRS complex. *End-systole* is more difficult to define. If ventricular septal motion is normal, end-systole may be represented at the nadir of septal motion. Normally, the interventricular septum and LV free wall move toward each other in systole and away from each other during diastole. However, peak motion may not correspond exactly because of the slight differences in myocardial depolarization. The septum is usually depolarized a few milliseconds before the free wall, causing it to contract sooner. When septal motion is abnormal, timing of the peak posterior wall motion can be selected. The end of the T wave has been described as a timing point, but this is generally inaccurate.

Measurements of *left ventricular chamber* and *walls* should be made at the level of the chordae tendineae. Normally, the LV wall is approximately three to four times thicker than the right. *Right ventricular chamber*

dimensions may vary according to whether the animal is in right or left lateral recumbency. *Aortic root* is measured at end-diastole. *Left atrium* is measured at end-systole at the maximal dimension (the standard M-mode long-axis parasternal view optimizing the LV outflow tract underestimates LA size).

ASSESSMENT OF CARDIAC CHAMBER SIZE, DIMENSIONS, AND STRUCTURES

The primary 2-D and M-mode imaging planes assess cardiac chamber dimensions, and related measurements help quantify systolic function. No single view provides all the information needed. Thus, multiple views should be obtained.

Determination of normal from abnormal structures requires the clinician to compare size relationships of cardiac structures visually, apply published normal values when available, and use personal experience. The range of normality is greater in the dog[38, 44–53] than in the cat due to the wider spectrum in canine size and weight. In the dog, relationships exist between certain echocardiographic mensurals, somatotype, and breed. Thus, charts listing "normal" values according to body size can be misleading and should be used only as a guide. They are most meaningful for dogs weighing between 14 and 22 kg than in the very small or large breeds. Although normal values have been recorded for some breeds (Table 8–1),[52–55] data are limited for the normal, immature animal and for extremes in body size and somatotype.[53, 56, 57]

Normal echocardiographic values have been reported for the cat (Table 8–2).[58–66] Although variation due to body weight has been described, it does not appear to be as great a problem as in the dog. However, because of the small size of the feline heart, suboptimal images frequently cause errors in measurement and interpretation.

Additional measurements have been reported, including amplitudes of motion (left septal echo or left ventricular free wall echo), the rate of rise or fall of the left ventricular free-wall echo, and others. Once the echocardiogram has been measured, it is assessed to identify abnormalities in chamber size, wall thickness and motion, valve morphology and motion, and indices of cardiac function.[1, 3]

THE MYOCARDIUM

Alterations in myocardial echogenicity can sometimes be assessed with 2-D echocardiography. The homogeneous appearance of the myocardium can be disrupted by diseases that produce hypoechoic areas (e.g., fluid-filled abscess from myocarditis or necrosis), mixed echoic areas (e.g., neoplasia such as a hemangiosarcoma), or hyperechoic regions (e.g., increased fibrous tissue or calcification, as sometimes occurs in papillary muscles with severe subaortic or pulmonic stenosis, or Duchenne's cardiomyopathy). Instrument settings must avoid excessive gain or reject, which could mimic or simulate myocardial lesions.

LEFT VENTRICLE

DILATION. This is associated with (1) volume overload (especially mitral regurgitation with chronic acquired valvular disease in dogs; aortic insufficiency; left-to-

TABLE 8–1
Normal Canine M-mode Echocardiography Values for Eight Different Breeds

Mensural	Miniature Poodle[52] (n = 20)*	English Cocker Spaniel[53] (n = 12)‡	Pembroke Welsh Corgi[52] (n = 20)*	Afghan Hound[52] (n = 20)*	Golden Retriever[52] (n = 20)*	Greyhound[54] (n = 16)‡	Deerhound[55a] (n = 21)‡	Irish Wolfhound[55] (n = 100)‡
Weight (kg)	3 (1.4–9)	12.2 ± 2.2	15 (8–19)	23 (17–36)	32 (23–41)	20.7–32.5	41.3 ± 4.9	>50
Heart rate (bpm)	150 (100–200)	—	120 (80–160)	120 (80–140)	100 (80–140)	—	125.7 ± 30	—
LVPWD (mm)	5 (4–6)	7.9 ± 1.1	8 (6–10)	9 (7–11)	10 (8–12)	12.1 ± 1.7	10.0 ± 1.8	9.5 ± 2.1
LVPWS (mm)	8 (6–10)	—	12 (8–13)	12 (9–18)	15 (10–19)	15.2 ± 2.2	15.3 ± 2.2	15.0 ± 3.3
LVD (mm)	20 (16–28)	33.8 ± 3.3	32 (28–40)	42 (33–52)	45 (37–51)	44.1 ± 3.0	51.2 ± 5.0	53.9 ± 5.2
LVS (mm)	10 (8–16)	22.2 ± 2.8	19 (12–23)	28 (20–37)	27 (18–35)	32.5 ± 3.5	34.0 ± 5.1	35.2 ± 4.8
FS (%)	47 (35–57)	34.3 ± 4.5	44 (33–57)	33 (24–48)	39 (27–55)	25.4 ± 6.3	33.5 ± 5.8	35.2 ± 4.9
EPSS (mm)	0 (0–2)	—	2 (0–5)	4 (0–10)	5 (1–10)	—	7.8 ± 1.6	7.4 ± 1.5
RVd (mm)	4 (2–9)	—	10 (6–14)	10 (5–20)	13 (7–27)	—	22.6 ± 5.7	26.7 ± 5.3
IVSd (mm)	5 (4–6)	8.2 ± 1.3	8 (6–9)	10 (8–12)	10 (8–13)	10.6 ± 1.7	9.1 ± 2.2	8.0 ± 1.9
IVSs (mm)	8 (6–10)	—	12 (10–14)	13 (8–18)	14 (10–17)	13.4 ± 2.5	14.6 ± 4.1	13.7 ± 3.4
AOD (mm)	10 (8–13)	—	18 (15–22)	26 (20–34)	24 (14–27)	—	29.6 ± 3.7	30.5 ± 4.0
LAS (mm)	12 (8–18)	—	21 (12–24)	26 (18–35	27 (16–32)	—	28.4 ± 3.9	33.7 ± 5.9

*Median (range).
LVPWD, LV posterior wall dimension at end-diastole; LVPWS, LV posterior wall thickness at end-systole; LVD, LV chamber dimension at end-diastole; LVS, LV chamber dimension at end-systole; FS, percent fractional shortening; EPSS, E-point septal separation; RVD, RV chamber dimension at end-diastole; IVSd, interventricular septal thicknesss at end-diastole; IVSs, interventricular septal thickness at end-systole; AOD, aortic root at end-diastole; LAS, left atrium at end-systole.
‡Mean ± standard deviation.

TABLE 8–2
Normal Feline M-mode Echocardiography Values*

Mensural	Fox et al[66] (n = 37)	Sisson et al[64] (n = 79)	Moïse et al[58] (n = 11)	Jacobs & Knight[60] (n = 30)	Fox et al[61] (n = 30)	Allen[63] (n = 10)‡	Soderberg et al[62] (n = 16)†	Pipers et al[59] (n = 25)
LVEDD (cm)	1.46 ± 0.20	1.5 ± 0.2	1.51 ± 0.21	1.59 ± 0.19	1.40 ± 0.13	1.29 ± 0.12	1.28 ± 0.17	1.48 ± 0.26
LVESD (cm)	0.82 ± 0.15	0.72 ± 0.15	0.69 ± 0.22	0.80 ± 0.14	0.81 ± 0.16	0.86 ± 0.16	0.83 ± 0.15	0.88 ± 0.24
Ao (cm)	0.95 ± 0.11	0.90 ± 0.14	0.95 ± 0.15	0.95 ± 0.11	0.94 ± 0.11	0.90 ± 0.07	0.94 ± 0.14	0.75 ± 0.18
LA (cm)	1.09 ± 0.18	1.17 ± 0.17	1.21 ± 0.18	1.23 ± 0.14	1.03 ± 0.14	1.03 ± 0.07	0.98 ± 0.17	0.74 ± 0.17
LA/Ao (cm)	—	1.25 ± 0.18	1.29 ± 0.23	1.30 ± 0.17	1.10 ± 0.18	—	1.09 ± 0.27	—
IVSED (cm)	0.37 ± 0.07	0.42 ± 0.7	0.50 ± 0.07	0.31 ± 0.04	0.36 ± 0.05	0.43 ± 0.03	—	0.45 ± 0.09
IVSES (cm)	—	0.67 ± 0.12	0.76 ± 0.12	0.58 ± 0.06	—	—	—	—
LVWED (cm)	0.36 ± 0.06	0.41 ± 0.07	0.46 ± 0.05	0.33 ± 0.06	0.35 ± 0.08	0.4 ± 0.04	0.31 ± 0.11	0.37 ± 0.08
LVWES (cm)	—	0.68 ± 0.11	0.78 ± 0.10	0.68 ± 0.07	—	—	0.55 ± 0.80	—
EPSS (cm)	—	0.06 ± 0.08	0.04 ± 0.07	0.02 ± 0.09	—	—	—	—
RVED (cm)	—	0.46 ± 0.17	0.54 ± 0.10	0.60 ± 0.15	0.50 ± 0.21	—	—	—
LVWA (cm)	—	—	0.50 ± 0.07	—	—	—	0.32 ± 0.11	—
AA (cm)	—	—	0.36 ± 0.10	—	—	—	—	—
MVEFS (mm/s)	—	—	54.5 ± 13.4	87.2 ± 26.0	—	—	83.78 ± 23.8	—
%FS	44.2 ± 8.2	52.1 ± 7.1	55.0 ± 10.2	49.8 ± 5.3	42.7 ± 8.1	34.05 ± 2.5	34.5 ± 12.6	41.0 ± 7.3
LVWT (%)	—	—	39.5 ± 7.6	—	—	—	95.1 ± 67.1	—
IVST (%)	—	—	33.5 ± 8.2	—	—	—	—	—
HR (beats/min)	—	—	182 ± 22	194 ± 23	245 ± 36	175 ± 19.9	—	167 ± 29
Body weight (kg)	4.8 ± 1.1	4.7 ± 1.16	4.3 ± 0.05	—	3.88 ± 1.17	3.6 ± 0.65	—	2.2 ± 6.5§
Age (years)	6.08 ± 3.6	5.1 (0.5–15)§	—	4.11 ± 1.05	3.36 ± 3.15	—	—	1.1 ± 5§

*Mean ± SD; †, sedated with ketamine HCl; ‡sedated wth pentobarbital; §normal range.
LVEDD, LV end-diastolic dimension; LVESD, LV end-systolic dimension; Ao, aortic root; LA, left atrium; LA/Ao, left atrium to aorta ratio; IVSED, intraventricular septum at end-diastole; IVSES, intraventricular septum at end-systole; LVWED, LV posterior wall at end-diastole; LVWES, LV posterior wall at end-systole; EPSS, E-point to septal separation; AA, aortic root amplitude; MVEFS, mitral valve E-F slope; %FS, % LV fractional shortening; LVWT, LV posterior wall thickening; IVST, interventricular septal thickening; HR, heart rate; —, not available.

right shunts such as patent ductus arteriosus or arteriovenous fistulas), (2) dilated cardiomyopathy, and (3) high-output states such as chronic anemia or thyrotoxicosis.

REDUCTION. The LV chamber size may be decreased with severe volume depletion as with severe dehydration, hypoadrenocorticism, or hypovolemic shock; or inadequate blood return to the LA and LV (e.g., heartworm disease, tetralogy of Fallot).

THINNING. Thin LV posterior wall segments may show aneurysms or infarction, as commonly observed in feline cardiomyopathies. Dilated cardiomyopathy may cause the ventricular septum and free wall to become relatively thin.

HYPERTROPHY. Left ventricular hypertrophy is associated with (1) pressure overloads (e.g., aortic stenosis, arterial hypertension), (2) cardiomyopathy (especially hypertrophic cardiomyopathy and endomyocardial fibrosis), (3) infiltrative myocardial diseases, and (4) hyperthyroidism.

WALL MOTION ABNORMALITIES. Hyperkinesis may occur with mitral or aortic insufficiency, certain volume overload states (e.g., severe anemia), hyperthyroidism, sympathetic stimulation, or hypertrophic cardiomyopathy. *Hypokinesis* may occur with dilated cardiomyopathy or diseases resulting in myocardial failure (e.g., doxorubicin cardiotoxicity, end-stage mitral insufficiency). *Akinesis* or *dyskinesis* may result from myocardial infarction. These abnormalities may be global or regional.

RIGHT VENTRICLE

DILATION. Dilation often results from RV volume overload (commonly, tricuspid insufficiency; uncommonly, atrial septal defects or severe pulmonic insufficiency) and cardiomyopathy (especially dilated cardiomyopathy, but occasionally hypertrophic or restrictive cardiomyopathy).

REDUCTION. The RV chamber size may be decreased with severe volume depletion or cardiac tamponade.

HYPERTROPHY. In dogs, RV hypertrophy usually results from right-sided heart pressure overloads (e.g., pulmonic stenosis, tetralogy of Fallot, cor pulmonale, heartworm disease, pulmonary thromboembolism, and idiopathic pulmonary hypertension). In cats, hypertrophic and restrictive cardiomyopathies can cause right-sided heart pressures to increase secondarily, with subsequent mild-to-moderate hypertrophy.

INTERVENTRICULAR SEPTUM

The septum is assessed for continuity (e.g., ventricular septal defects), abnormal relationships between the

septum and other cardiac structures (e.g., overriding aorta in tetralogy of Fallot), and patterns of hypertrophy, thinning, and motion.

HYPERTROPHY. Most commonly, septal hypertrophy results from hypertrophic cardiomyopathy or disorders increasing left or right ventricular afterload (e.g., aortic or pulmonic stenosis, hypertension). In feline hypertrophic cardiomyopathy, the septum may be diffusely or segmentally hypertrophied.

THINNING. A diffusely thin septum typically accompanies dilated cardiomyopathy. Regional thinning may occur with feline myocardial disorders, infarction, or aneurysms.

SEPTAL MOTION ABNORMALITIES. These may reflect abnormal filling and depolarization patterns of the left and right ventricles. In LV volume overload (e.g., severe mitral insufficiency), ventricular septal motion may be hyperkinetic; during early diastole, marked anterior (i.e., toward the transducer) movement may occur from excessive inflow of blood. Conversely, in right ventricular pressure or volume overload, interventricular septal motion may be reduced, or its motion may be paradoxic relative to the left ventricular free wall. *Paradoxic septal motion* is recognized when the septum moves anteriorly (toward the transducer) instead of posteriorly (away from the transducer) during systole. In pure RV volume overload (e.g., tricuspid insufficiency), septal flattening and paradoxic motion occurs during diastole; in systole, the LV resumes a normal circular appearance. However, with pure RV pressure overload or in RV pressure and volume overload, the septum remains flattened during systole and diastole, conferring a half-moon shape to the left ventricle (Fig. 8–11).

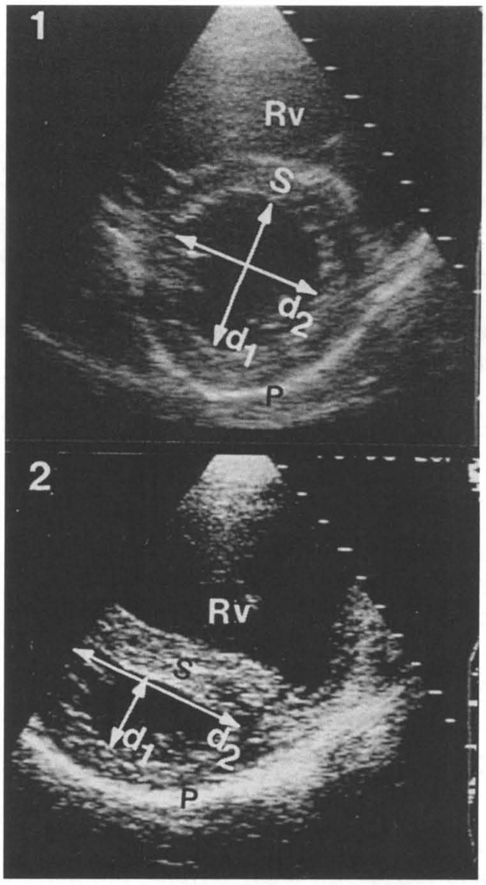


FIGURE 8–11

Two-dimensional echoes from two dogs obtained in the right parasternal transducer location. These short-axis views are at the level of the chordae tendineae recorded in diastole. *Frame 1:* Healthy, 35-kg Chesapeake Bay retriever demonstrating normal circular left ventricular geometry. The two perpendicular left ventricular minor axis dimensions (d_1 and d_2) were equal in both systole and diastole. *Frame 2:* 6-year-old, 32-kg German shepherd with heartworm disease and associated pressure and volume overload. The two dimensions are unequal during systole and diastole. Note the flattened interventricular septum *(S)*. *Rv,* right ventricle; *P,* pericardium.

LEFT AND RIGHT ATRIA

The atria are evaluated for dilation, intracavitary masses (e.g., thrombi or neoplasia), or abnormal septation. In the four-chamber view, the normal left and right atria are approximately the same size.

LEFT ATRIAL ENLARGEMENT. The long-established M-mode comparison of the aortic diameter at end-diastole to the LA at its maximal systolic excursion has value if the exact location of the left atrial transection is known. Blinded examination may actually provide a scan of the left auricle or pulmonary artery rather than the body of the LA. The best appreciation of left atrial size is attained from right parasternal short-axis views by 2-D echocardiography. Measuring LA circumference in one or more planes may provide a means of accurately comparing size between examinations. The LA enlarges in dogs most commonly with chronic, acquired mitral regurgitation and dilated cardiomyopathy, and less frequently, congenital left-to-right shunts (e.g., PDA), mitral stenosis, and cor triatriatum. In cats, LA enlargement occurs most commonly from myocardial diseases, mitral valve malformation, and hyperthyroidism.

RIGHT ATRIAL ENLARGEMENT. The RA enlarges in dogs most commonly with tricuspid regurgitation, dilated cardiomyopathy, or heartworm disease. Less common causes include tricuspid stenosis, congenital right-to-left shunts, cor pulmonale, and pulmonary hypertension. In cats, enlargement most commonly results from myocardial disease. Less frequent causes are tricuspid regurgitation (tricuspid dysplasia), heartworm disease, or hyperthyroidism.

ATRIAL SEPTUM

The atrial septum may bulge into either atrium in cases of severe pressure or volume overload. An intact atrial septum can be verified using two-dimensional and Doppler echocardiographic imaging, as well as contrast echocardiography.

PULMONARY ARTERY AND AORTA

Identification of the pulmonary artery is usually possible only with 2-D imaging. Normally, the pulmonary trunk is slightly smaller than the aortic root. It is dilated with congenital left-to-right shunts, pulmonic stenosis, heartworm disease, or cor pulmonale.

The aorta may be reduced in size when forward cardiac output is decreased. The ascending aorta may be enlarged with subaortic stenosis (associated with poststenotic dilatation), with tetralogy of Fallot, and in some old, or hypertensive cats. Aortic dilation occurs at and just distal to the juncture of a patent ductus arteriosus.

CARDIAC VALVES

The four cardiac valves are directly evaluated for motion, excursion, and structure. Changes in cardiac chambers may result from valvular problems such as cardiac chamber enlargement with severe valvular insufficiency or ventricular hypertrophy with valvular stenosis. Doppler echocardiographic transvalvular flow profiles are altered according to the specific valve lesions.

ATRIOVENTRICULAR VALVES. The normal sequence of mitral valve opening and closing is shown in Figure 8–1. A variety of lesions may affect AV valves (Fig. 8–12; see also Fig. 8–21). These leaflets should appear as smooth, echodense, fine lines. Irregularities, masses, or thickening may indicate myxomatous valve degeneration (endocardiosis) or vegetative endocarditis. In aortic valvular insufficiency, the regurgitant jet may strike the anterior mitral valve leaflets, causing them to exhibit fine diastolic fluttering. In AV valvular prolapse, ruptured chordae tendineae, or severe endocardiosis, the AV valves may be seen within the corresponding atria during systole. Rupture of chordae tendineae can cause a flail leaflet. In mitral valve stenosis, valve leaflets will be thickened and display decreased E to F slope. The posterior leaflet will have abnormal anterior motion during early diastole. In systolic anterior motion of the anterior mitral valve, this leaflet makes a sharp-angled bend against the basilar ventricular septum during systole.

SEMILUNAR VALVES. The aortic and pulmonic valves are best imaged with 2-D echocardiography. Three leaflets of the aortic valve may be identified on a 2-D short-axis view, although only two leaflets of the pulmonic valve are evident from this imaging plane. Aortic valve opening and closing may be altered in many conditions, and this is well demonstrated by M-mode echocardiography (Fig. 8–13). The aortic valve may exhibit fine systolic fluttering on an M-mode scan from high blood flow in both normal and pathologic conditions. Normally the leaflets should exhibit a wide systolic opening excursion, appearing parallel to the vessel wall in 2-D echo or as a "box suspended on a string" on M-mode. Premature aortic valve closure indicates ventricular outflow obstruction and is most common with the obstructive form of feline hypertrophic cardiomyopathy and with some cases of congenital subaortic stenosis. Early aortic valve closure may also occur with low-flow states and poor cardiac output. Thickened aortic valve leaflets may occur with endocardiosis and may be accompanied by Doppler evidence of regurgitation. Vegetative endocarditis may restrict aortic valve opening and cause masslike lesions on valve leaflets; these may prolapse into the left ventricle during diastole. If leaflet doming occurs, valvular stenosis may be present.

PERICARDIUM

The pericardium is normally evident as the brightest line adherent to the pericardial surface. With pericardial effusion, an echolucent, or "echo-free," space is created between the epicardium and pericardium (see later). Occasionally, fibrin or neoplasia will cause the effusion to be echogenic. The presence of pleural effusion will clearly highlight the pericardium, which is contrasted between two bodies of effusion.

EVALUATION OF CARDIAC FUNCTION

There is no universally satisfactory method to evaluate cardiac function. Each parameter and technique has certain strengths and weaknesses. They should be interpreted in the context of their inherent limitations and in conjunction with clinical information from the physical examination and complete data base.[1, 1a]

CARDIAC SIZE

The size of ventricular chambers reflects the degree of volume overload or, frequently, the severity of some forms of cardiomyopathy. Cardiac chamber dimensions can be readily determined by M-mode and 2-D

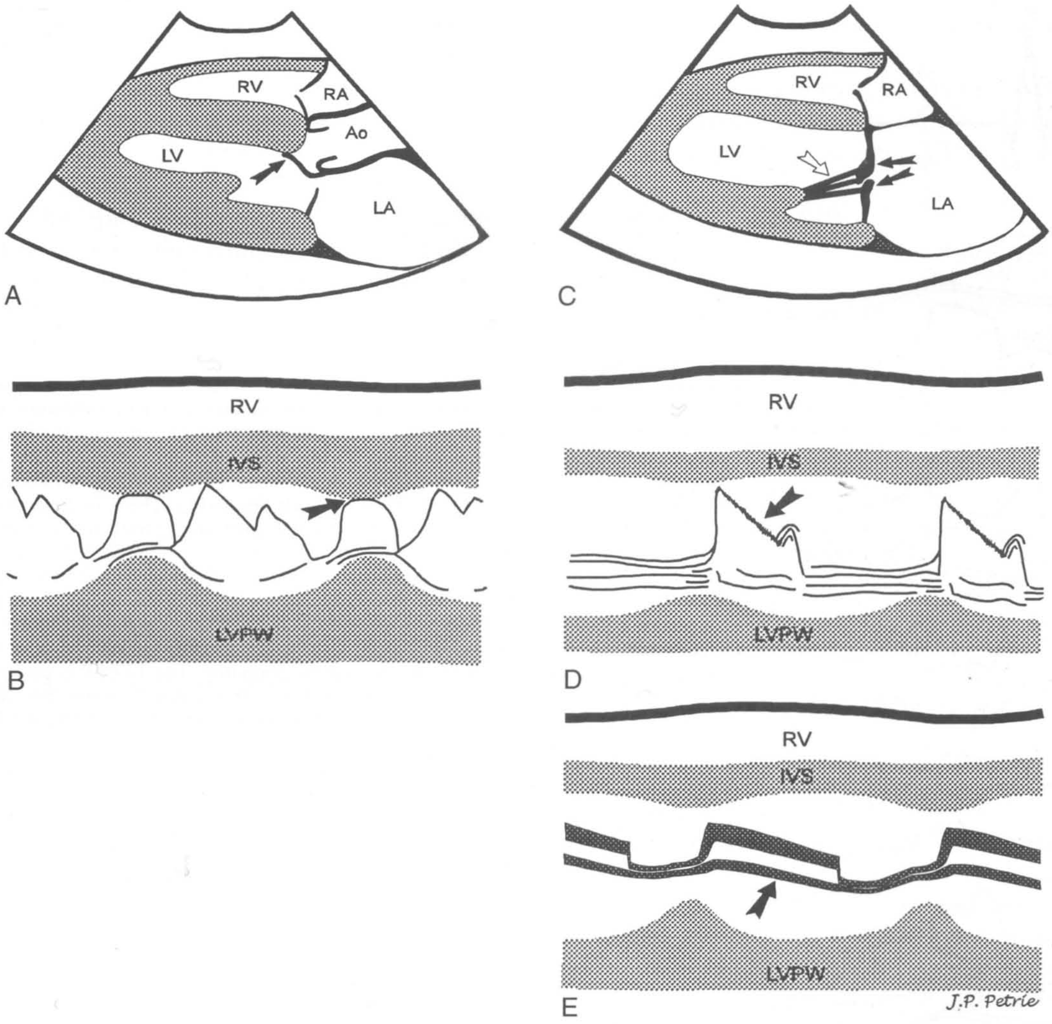


FIGURE 8–12

Common abnormalities of the mitral valve. (A) and (B) Cat with hypertrophic cardiomyopathy and systolic anterior motion of the mitral valve. (A) is a 2-D parasternal long-axis view optimizing the left ventricular *(LV)* outflow tract and the left atrium *(LA)*, and (B) is an M-mode echo at the mitral valve level: during systole, the anterior mitral valve leaflet makes a sharp-angled bend *(arrow)* across the LV outflow tract, shown in (A), to coapt against the basilar ventricular septum during systole (B). (C) 2-D right parasternal four-chamber view of a dog with chronic acquired valve disease. The mitral valve leaflets *(black arrows)* are thickened and protrude into the left atrium during systole; associated chordae tendineae *(open arrow)* are also thickened. (D) M-mode tracing at the mitral valve level of a dog with moderate aortic insufficiency; this regurgitant jet strikes the anterior mitral valve leaflet during diastole when the mitral valves are open, causing the leaflet to exhibit fine diastolic flutter *(arrow)*. (E) M-mode trace at the mitral valve level of a dog with mitral valve stenosis. Note the thickened leaflets; decreased E to F slope [compare with (B) and (C) above]; and abnormal early diastolic cranial motion *(arrow)* exhibited by the posterior mitral leaflet, which probably indicates fusion of the valve commissures (normally, the posterior leaflet moves away, or downward from the anterior leaflet). *RV,* right ventricle; *Ao,* aortic root; *IVS,* interventricular septum; *LVPW,* left ventricular posterior (free) wall. (Courtesy of Dr. J. P. Petrie, The Animal Medical Center.)

echocardiography and can be used to estimate ventricular volumes.

E-POINT SEPTAL SEPARATION (EPSS). A rough assessment of LV size is to measure the distance from the E point of the anterior mitral valve leaflet to the interventricular septum. Normally, there is none or very minimal separation (see Tables 8–1, 8–2). As LV ejection fraction decreases, EPSS increases. Limitations include the assumption of normal mitral valve motion and the necessity for correct (perpendicular) ultrasound beam alignment through the ventricular septum, mitral valve, and free wall.

LEFT VENTRICULAR VOLUMES

In a study of a small group of dogs with chronic acquired valve disease, LV end-systolic volume index

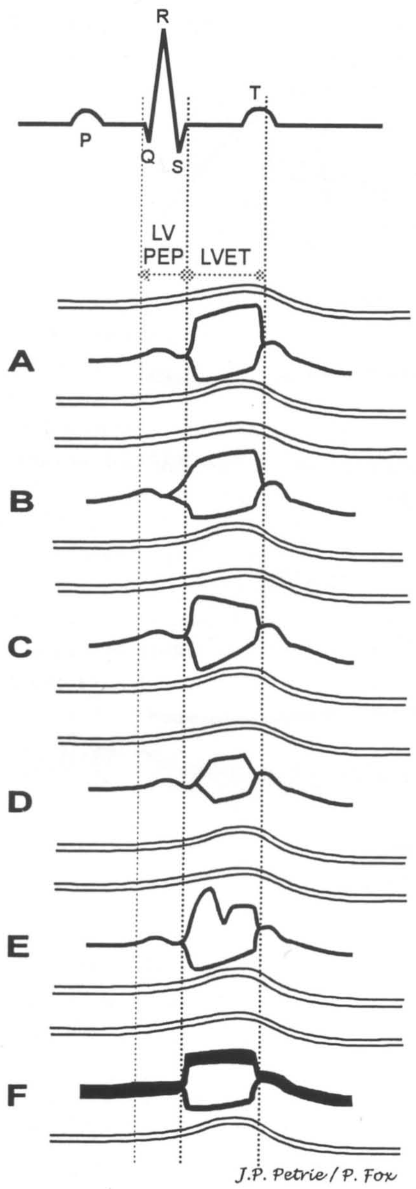


FIGURE 8–13

M-mode echo traces illustrating abnormalities of the aortic valve. (A) Normal pattern of valve excursion. The aortic valves typically open abruptly, remain open during LV systolic ejection, then close abruptly, simulating a "box suspended on a string." The timing of this sequence is correlated with a simultaneously recorded electrocardiogram above, which facilitates assessing systolic time intervals (consult Fig. 3–14). These include the LV pre-ejection period *(LVPEP)*, representing the interval from the Q wave to the aortic valve opening, and the LV ejection time *(LVET)*. (B) Premature opening of the aortic valve (before onset of electrical depolarization) associated with severely elevated LV end-diastolic pressure secondary to severe aortic regurgitation. (C) Premature leaflet closure in a dog with severe mitral regurgitation and myocardial failure. Leaflets separate normally with onset of LV ejection but gradually close during systole. (D) Greatly attenuated valve dynamics due to severe myocardial failure from dilated cardiomyopathy. The LVPEP is prolonged and LVET is shortened. Aortic valve opening is delayed, the duration of ejection and maximal valve excursion are diminished, and the valves close prematurely. (E) Midsystolic closure of the aortic valve. During midsystole, the aortic valves close secondary to the subvalvular obstruction associated with systolic anterior motion of the mitral valve (see Fig. 8–12 *A,B*). (F) Vegetative endocarditis involving the aortic valves. Increased echoes are apparent on the valve leaflets, without restriction of valve motion. Vegetations may be best imaged in diastole or systole, depending on the direction of the ultrasound beam.

increased linearly with LV end-diastolic volume index. An index is derived by dividing the calculated volume by patient body surface area. The Teichholz method,

$$\text{Volume} = [7.0/2.4 + D] \times D^3$$

where D equals the left ventricular internal dimension, calculated the largest LV end-systolic volume (compared with using D^3, or $1.2 \times D^3$ for calculations). The end-systolic volume index (normal, less than 30 ml/m^2) more accurately separated out dogs with mitral insufficiency and myocardial failure than did shortening fraction; end-diastolic volume index was more than 100 ml/m^2 (normal, less than 100 ml/m^2), indicating volume overloading.[67, 68]

Many models and formulas have been described for calculating LV volume.[69] Certain geometric assumptions inherent in the various formulas and technical considerations introduce error in echocardiographic calculation of chamber volumes. A more accurate method employs Simpson's rule (also known as the "disc summation method"), which calculates the sum of volumes of a series of smaller, similar figures.

LEFT VENTRICULAR MASS

An important adaptation to LV pressure or volume overload is muscular hypertrophy. This is grossly characterized by increased LV muscle mass or weight, and it is determined by increased wall thickness and/or chamber volume. A number of echocardiographic methods have been reported to calculate LV mass (LVM) but are based on the assumption that myocardial volume equals the total volume contained within

epicardial borders of the ventricle, minus the LV chamber volume[69]:

$$LVM = [V_T(ep) - V_c(en)] \times 1.05$$

where V_T is the total LV volume, or the volume contained within the epicardial interface, and V_c is the chamber volume, or volume contained within the endocardial interface. The ventricular septum is assumed to be part of the LV. Volume components of LV mass formulas can be calculated by formulas for deriving LV volumes (see previous section). Accuracy is influenced by formulas and measurement acuity. When there is widely varying LV wall thickness, it is difficult to establish representative dimensions.

EJECTION PHASE INDICES OF LEFT VENTRICULAR PERFORMANCE

These indices represent the most commonly used clinical measurements of LV systolic function and are largely derived from linear dimensions described earlier (Tables 8–1 to 8–3). Although generally considered to reflect myocardial contractility, each is influenced by ventricular loading conditions. Thus, if preload (LV end-diastolic volume) or afterload (LV end-systolic volume) is reduced, or if aortic pressure (afterload) is increased, ejection phase indices decline (and vice versa).

STROKE VOLUME (SV). The SV is computed as:

$$SV = \text{LV end-diastolic volume (EDV)} - \text{LV end-systolic volume (ESV)}$$

Both volumes are calculated using one of the many methods for chamber volume calculation (see earlier). Stroke volume normally decreases during inspiration.

EJECTION FRACTION (EF). The EF, a global index of LV fiber shortening, is a highly regarded measure of LV systolic function in humans, in whom it has been thoroughly validated. It is the ratio of the LV stroke volume to the LV end-diastolic volume (EDV):

$$EF = \frac{EDV - ESV}{EDV} \times 100$$

In one study of dogs with chronic mitral regurgitation, echo-derived EF was useful to separate dogs with normal or mild from severe myocardial failure.[67]

PERCENT FRACTIONAL SHORTENING (%FS, OR %ΔD). Derived from M-mode recordings of the LV minor axis, the %FS can be calculated as:

$$\%FS = \frac{LVDd - LVDs}{LVDd} \times 100$$

where the LVDd is the LV chamber diameter at end-diastole, and LVDs is the LV chamber diameter measured at end-systole. This index is based upon angiographic observations that the systolic decrease in LV ventricular volume results primarily from minor axis shortening, and it represents a simple method for estimating ventricular function in the symmetrically contracting ventricle.

The %FS has certain limitations. Major changes in ventricular morphology often occur near the LV apex and remain unaccounted for by %FS. In addition, %FS is dependent on inherent cardiac contractility, preload, and afterload. With canine chronic acquired valve disease (mitral insufficiency), the LV experiences decreased afterload as the incompetent mitral valve permits the LV to eject blood retrogradely into the low-pressure left atrium, rather than into the high-pressure aorta. Thus, even though a higher %FS results than if the heart did not have mitral insufficiency, this does not mean that the inherent contractility is

TABLE 8–3
Normal Left Ventricular Systolic Time Intervals*

	Canine		Feline			
Parameter	*Atkins & Snyder*[71] *(n = 20)*	*Pipers et al*[59] *(n = 25)*	*Atkins & Snyder*[71] *(n = 6)*	*Jacobs & Knight*[60] *(n = 30)*	*Fox et al*[61] *(n = 27)*	*Pipers et al*[51] *(n = 10)*
PEP (ms)	54 ± 7	69 ± 8	46 ± 5	—	44 ± 9	—
LVET (ms)	159 ± 15	256 ± 13	116 ± 19	140 ± 20	116 ± 11	150 ± 20
LVETI (ms)†	227 ± 15	301 ± 10	206 ± 9	—	214	217
PEP/LVET	0.34 ± 0.05	0.24 ± 0.09	0.40 ± 0.05	—	0.38 ± 0.08	—
QAVC (ms)	214 ± 18	324 ± 7	162 ± 24	—	—	—
VcF (circ/sec)	2.48 ± 0.50	—	4.0 ± 0.9	3.7 ± 0.6	3.5 ± 0.8	2.9 ± 0.8
Heart rate (bpm)	124 ± 23	81 ± 7	226 ± 25	194 ± 23	245 ± 36	167 ± 7

*Mean ± SD.
†Calculated for dogs: LVET + 0.55 (heart rate)[51]: for cats, LVET + 0.40 (heart rate).[60]
PEP, pre-ejection period; LVET, left ventricular ejection time; LVETI, LV ejection time index; QAVC, duration from ECG Q-wave to aortic valve closure; VcF, velocity of circumferential fiber shortening; circ, circumference; bpm, beats per minute.

increased or even normal. Shortening fractions less than 50 percent and EDV indices greater than 200 ml/m^2 may indicate myocardial failure when severe mitral insufficiency is present.[67]

CIRCUMFERENTIAL FRACTIONAL SHORTENING (V_{cf}). This index, expressed in circumferences per second, is calculated as:

$$V_{cf} = \frac{LVDd - LVDs}{LVDd \times LVET}$$

where LVET is the LV ejection time calculated from systolic time intervals (see later). When derived from M-mode echo measurements, V_{cf} actually represents the velocity of shortening of the minor axis and not the whole circumference.

LEFT VENTRICULAR WALL STRESS

The aforementioned noninvasive measures of LV systolic function do not differentiate between abnormalities of myocardial contractility and changes in preload or afterload (loading conditions). A method to overcome these limitations utilizes measurement of LV wall stress (measured as dynes/cm^2), which incorporates end-systolic stress length and end-systolic pressure-volume relations. A simplified index of end-systolic meridional wall stress is calculated as follows:

$$\frac{PR}{W} = P\,\frac{\left(\frac{LVID}{2}\right)}{W}$$

where P is LV pressure (can be estimated by arterial blood pressure determination), R is minor LV radius, W is LV wall thickness, and LVID is LV diameter.[70] These and other formulas have not been clinically validated in veterinary heart failure patients.

SYSTOLIC TIME INTERVALS

Systolic time intervals (STI) assess global LV systolic performance. Although they are affected by heart rate, preload, and afterload, they are readily measured by simultaneous recording of the ECG and M-mode echocardiogram of the aortic valve (Fig. 8–13). The *pre-ejection period (PEP)* represents the time between initial inflection of the QRS (Q wave) and the onset of LV ejection, which is marked by opening of the aortic valves. The *LV ejection time (LVET)* is measured from the aortic valve opening to its closure. *Total electromechanical systole* (QAVC interval) represents the interval from initiation of the QRS complex to aortic valve closure (e.g., sum of the PEP and LVET). Alternatively, LVET can be measured as representing the time of the first anterior motion of the LV free wall to the point of its peak excursion[61]; LVET can also be measured as the duration of the Doppler echo signal at the aortic valve. The PEP/LVET index is superior to either index alone as it compensates somewhat for effects of loading conditions and heart rate. Normal values for STIs are listed in Table 8–3.[51, 59–61, 71]

HEMODYNAMIC INFORMATION

Echocardiography can provide quantitative data about blood flow and intracardiac pressures.[72] The mean blood flow velocity through a vessel or valve orifice is acquired by measuring the velocity-time integral of the Doppler signal (i.e., the area under the Doppler recording trace). The corresponding cross-sectional diameter is measured by 2-D or M-mode echocardiography and the area is calculated. For example, blood flow in the ascending aorta and cross-sectional area may be used in this fashion to calculate cardiac output (CO):

$$CO = A \times V \times HR$$

where A = area of vessel or orifice, V = integrated flow velocity, and HR = heart rate. A number of technical limitations affect accuracy, particularly in obtaining an accurate orifice area. However, Doppler techniques for measuring cardiac output or stroke volume have the potential for following directional changes in a given patient.

DIASTOLIC FUNCTION

Diastolic function encompasses several distinct and fundamentally different hemodynamic phases. Although many parameters have been proposed to measure its various aspects, no single index is universally applicable or even ideal.[72a]

A number of diastolic indices have been derived from M-mode echo tracings. They include measurements that assess time periods (*diastolic time intervals*), and those that measure rates of change of different dimensions. Some of the more commonly used assessments include the isovolemic relaxation period, relaxation time index, peak or rate of change in LV dimension, duration of rapid filling phase (i.e., the time from minimum LV dimension to the moment when the rate of increase in dimension has decreased to 20% or 50% of its maximum value), time to peak filling rate, and peak rate of ventricular wall thinning in diastole.[1, 3] In the normal dog or cat, LV relaxation causes a rapid and smooth descent from the nadir during systole to the point of greatest chamber dimen-

sion in diastole. However, with diastolic dysfunction, normal wall descent may be interrupted by a bump or ridge evident on the LV posterior wall.

M-mode atrioventricular valve tracings parallel events recorded by spectral Doppler echocardiography. For example, maximum M-mode AV valve excursion reflects similar dynamics as recorded by diastolic transmitral blood flow velocity during Doppler echo examination. Similarly, the appearance of abnormal mitral valve closure (i.e., decreased E to F slope), as seen with mitral valve stenosis, reflects the spectral Doppler profile recorded during prolonged ventricular filling.

Doppler transmitral flow profiles are affected by ventricular compliance and relaxation. Accordingly, time-velocity Doppler signals generated during early diastolic flow (E wave) and flow following atrial systole (A wave) may be altered with LV diastolic dysfunction (Fig. 28–2).[72a] Normally, the peak E-wave velocity exceeds the peak A-wave velocity (E/A ratio >1). In certain diseases, early peak diastolic flow is reduced and peak flow following atrial contraction is greatly increased, decreasing the E/A ratio less than 1, and representing the "delayed relaxation" pattern. Other alterations have been described, including increased peak E-wave velocity and decreased (often minuscule) peak A-wave velocity, representing the so-called "restrictive" pattern. A variety of other measurements evaluating different portions have been reported, including peak acceleration and deceleration velocities and velocity-time integrals. It is important to note that these velocity alterations are not disease specific but are present in disorders that share similar diastolic properties. Moreover, many technical factors may affect transvalvular dynamics, including age, phase of respiration, heart rate, and precise Doppler sampling site.

ABDOMINAL IMAGING

Ultrasonic examination need not stop at the diaphragm. Normal sonographic anatomy of the liver is easily identified[73] as are changes associated with heart failure (Fig. 8–14). The presence of a dilated caudal vena cava, dilated hepatic vessels, enlarged and rounded liver, or ascites may help provide evidence for right-sided congestive heart failure.

INTERPRETATION OF THE DOPPLER ECHOCARDIOGRAM

Doppler echocardiography evaluates blood flow dynamics by directing the ultrasound beam parallel to blood flow (Fig. 8–15); ultrasound waves reflect off moving RBCs and are processed into a spectral trace (in contrast, 2-D echocardiography illustrates cardiac structures by directing the echo beam perpendicular to tissues). Doppler echo examinations use similar "windows" (transducer positions) as in 2-D imaging, but specific views are selected, such as the left apical window (Fig. 8–15), to provide the most parallel beam alignment to blood flow.

INDICATIONS FOR DOPPLER ECHOCARDIOGRAPHY. The greatest application of Doppler echocardiography is in diagnosis and evaluation of congenital heart disease. The answer to the question, "When is a routine Doppler examination warranted with acquired heart disease," is not always clear. Ideally, Doppler echocardiography studies should provide new information—that is, detect an unsuspected lesion, exclude a lesion believed to be present, or detect a transvalvular gradient.[1]

A complete Doppler echo examination should include assessing all cardiac valves from right and left parasternal positions. It is often performed in conjunction with and following a 2-D echocardiographic study. The tendency to focus only on areas suspected for high diagnostic yield may actually result in lesions being overlooked.

Examples of Doppler echocardiograms in acquired and congenital heart disease are illustrated in Figures

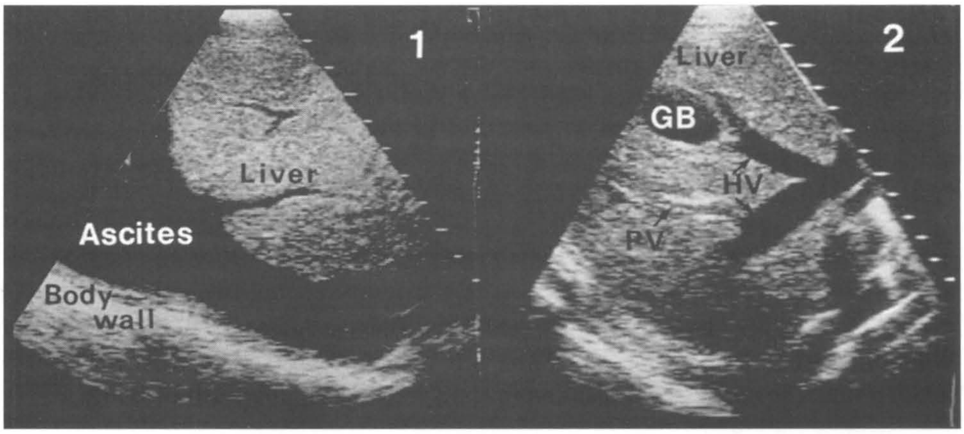


FIGURE 8–14

Two-dimensional abdominal sonograms from dogs with right-sided congestive heart failure. *Frame 1* shows ascites and hepatomegaly with rounded liver edges. *Frame 2* illustrates passive hepatic congestion. Hepatic veins *(HV)* are markedly enlarged compared with the portal veins *(PV)*, which characteristically have more echogenic walls. GB, gallbladder.

8–4, 8–5, 8–15, 8–16, 8–18; see also Figures 24–1, 24–9, 24–16, 24–26*B*, 24–32*A*, 24–38, 24–56*D*, 28–2, 28–4, and 28–5. Normal blood flow velocities across the cardiac valves are listed in Table 8–3.[74] The physics and practical use of quantitative Doppler echo[75, 76] and color-flow Doppler[77, 78] have been published. Normal values for Doppler echocardiography parameters are listed in Table 8–4.[74, 79–81]

QUANTIFICATION OF VALVULAR REGURGITATION

Many methods have been proposed for estimating the severity of valvular regurgitation, but true quantification remains elusive.[82] Although color-flow Doppler mapping provides a spatiotemporal display of the regurgitant jet, there are significant limitations related to cardiac geometry and Doppler technology. Quantitative color-flow analyses have utilized two approaches to evaluate regurgitant jets. One considers the momentum flux of the distal jet, which relates factors including jet length, area, and valve orifice area to severity. Clinically, semiquantification of severity is approximated by the size, length, and configuration of the regurgitant jet.[1] Severity is generally graded mild, moderate, or severe. The other approach applies principles of flow convergence, which analyze velocities upstream from the regurgitant orifice.[83] If only pulsed-wave Doppler echocardiography is available, semiquantification is obtained by first placing the sample volume in the center of valve orifice, then gradually moving it outward in an expanded radial sweep to define the limits of regurgitation.

ECHOCARDIOGRAPHIC DIAGNOSIS OF CONGENITAL HEART DISEASE

Many congenital heart defects may be specifically diagnosed or strongly suspected on the basis of two-dimensional echocardiographic examination. Doppler echocardiography provides important data for such diagnosis and characterization.

PATENT DUCTUS ARTERIOSUS

The PDA communicates between the descending aorta and the main pulmonary artery (see Figs. 1–4, 1–5). It may be identified in the short-axis view (Fig. 8–16). The aortic arch may be imaged from a subcostal (see Fig. 24–44) or cranial left parasternal position.

LEFT-TO-RIGHT–SHUNTING PDA. Nonspecific 2-D echocardiographic changes may include (1) those associated with a chronic, severe left heart volume overload, including LA and LV dilation and increased mitral valve E-point septal separation; right heart dilation may develop secondarily; (2) mildly reduced fractional shortening or a value in the low-normal range; (3) exaggerated interventricular septal motion; and (4) enlargement of the aorta and main pulmonary artery. Color-flow Doppler mapping is very helpful in demonstrating this anomalous vascular shunt. During diastolic runoff from the descending aorta into the main pulmonary artery, it codes blood flow in the ductus as red (i.e., flowing toward the transducer).[84] Pulsed-wave

TABLE 8–4
Normal Spectral Doppler Echocardiography Velocities (cm/sec)*

	Feline *Fox et al*†§	Feline *Santilli & Bussadori*‡§	Canine *Brown et al*[74]§	Canine *Gaber*[79]	Canine *Yuill & O'Grady*[80]‖	Canine *Kirkberger et al*[81]§	Canine *Kirkberger et al*[81]‖
Mitral Valve							
E wave	—	66 ± 11	—	75.0 ± 11.8	86.2 ± 9.5	91 ± 15	94 ± 16
A wave	—	52 ± 8	—	53.8 ± 8.7	—	63 ± 13	64 ± 15
EA wave	87 ± 9	—	—	—	—	—	—
Tricuspid Valve							
E wave	—	—	—	56.2 ± 16.1	68.9 ± 8.4	86 ± 20	85 ± 20
A wave	—	—	—	—	—	58 ± 16	58 ± 17
EA wave	88 ± 14	—	—	—	—	—	—
Pulmonary Valve	102 ± 15	—	84.0 ± 17	99.8 ± 15.3	R 98.1 ± 9.4 L 95.5 ± 10.3	120 ± 20	125 ± 26
Aortic Valve	102 ± 19	—	106 ± 21	118.9 ± 17.8	118.1 ± 10.8	157 ± 33	149 ± 27

*Mean (cm/sec) ± SD.
†Fox PR, et al. Unpublished data, 1996.
‡Santilli RA, Bussadori C. Unpubished data, 1996.
§Velocities measured by pulsed-wave Doppler echocardiography.
‖Velocities measured by continuous-wave Doppler echocardiography.
R, values derived from right parasternal short-axis view; L, values derived from left parasternal long-axis view.

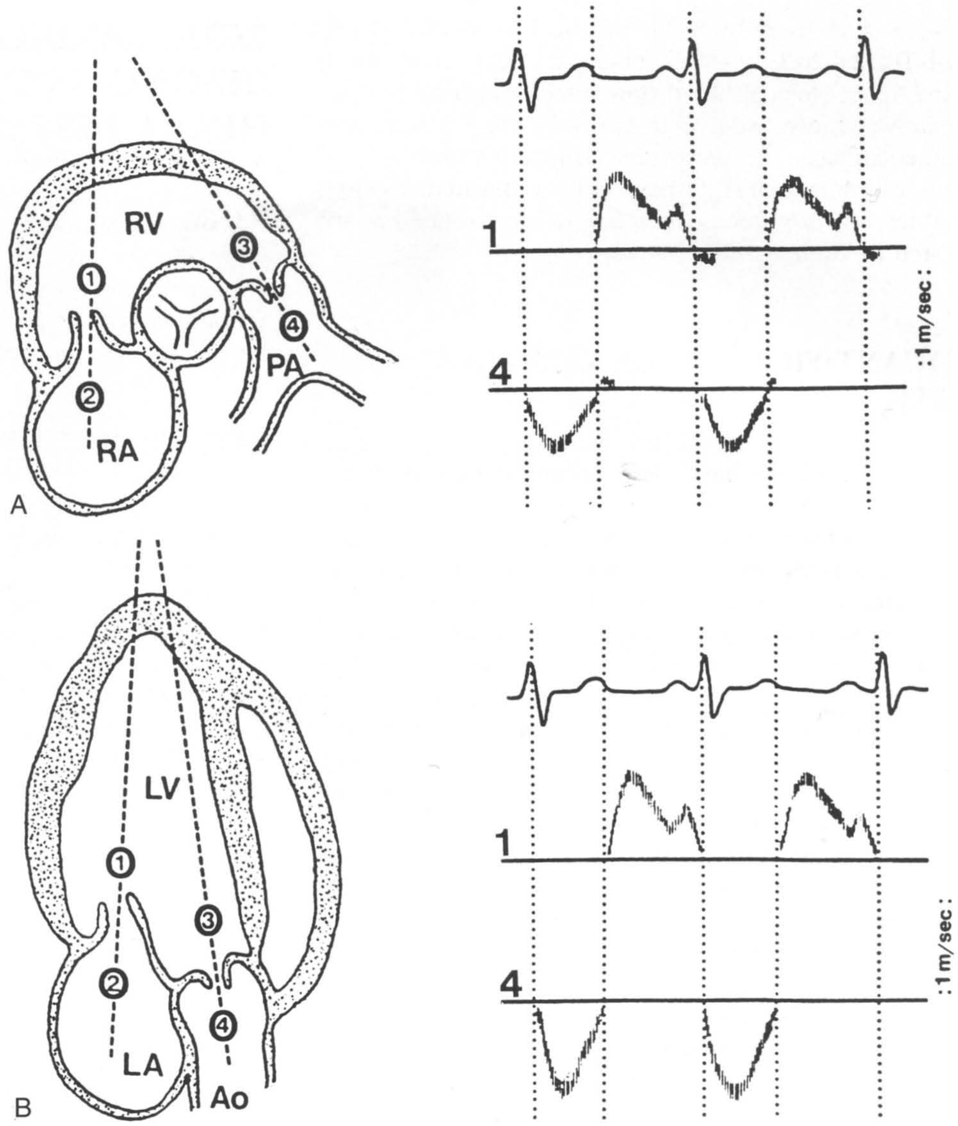


FIGURE 8–15

(A) Cranial parasternal short-axis view at the level of the aorta, with pulsed-wave sample sites on either side of the tricuspid *(1, 2)* and pulmonic *(3, 4)* valves. The grid illustrates spectral Doppler recording: *1*, normal tricuspid diastolic flow; *4*, normal pulmonic systolic flow. Site 2 would detect tricuspid regurgitation, and site 3, pulmonic regurgitation. (B) Left apical two-chamber view with pulsed-wave Doppler sample sites on either side of the mitral *(1, 2)* and aortic *(3, 4)* valves. The grid illustrates spectral Doppler echo recordings: *1*, normal mitral diastolic flow; *4*, normal aortic systolic flow. Site 3 would detect aortic regurgitation, and site 2, mitral regurgitation. (From Kisslo J, Adams D, Mark DB. Basic Doppler echocardiography. Clin Diagn Ultrasound 17:78–87, 1986, with permission.)

Doppler echocardiography can verify (1) turbulent flow through the main pulmonary artery, (2) abnormal retrograde (Fig. 8–16*B*) and continuous (Fig. 8–16*D*) flow in the main pulmonary artery, and (3) mild increases in transmitral (usually <1.75 m/sec) and aortic (usually <2.5 m/sec) flows. After successful ductal ligation or occlusion, normal laminar flow within the pulmonary artery is re-established.

RIGHT-TO-LEFT–SHUNTING ("REVERSED") PDA. A dilated pulmonary artery and ductal communication may be imaged with associated changes of increased pulmonary vascular resistance, including right ventricular hypertrophy and paradoxic interventricular septal motion. Contrast echocardiography causes opacification of the descending aorta but not the left ventricle. The former is best visualized as it courses over the bladder. Doppler studies can identify turbulence at the junction of the ductus and descending aorta where the flow disturbance is localized. Complete right-to-left shunting through the PDA is rare, however. Even with suprasystemic pulmonary artery pressures, some diastolic flow is usually detected. Other nonspecific findings include evidence of pulmonary hypertension, including high-velocity tricuspid and pulmonic regurgitation; pulmonic blood flow with a decreased time to peak velocity; abrupt decrease in flow velocity in midsystole; loss of a normal negative presystolic velocity component of pulmonic flow corresponding to atrial systole; and indicators of decreased right ventricular compliance (early ventricular diastolic filling velocity that is less than that produced with atrial systole).[85]

Several conditions may have spectral Doppler blood flow patterns that can be confused with PDA. These include anomalous origin of a coronary artery, aortic pulmonary window, and pulmonic insufficiency. Color-flow Doppler mapping greatly facilitates their differentiation.[85–87]

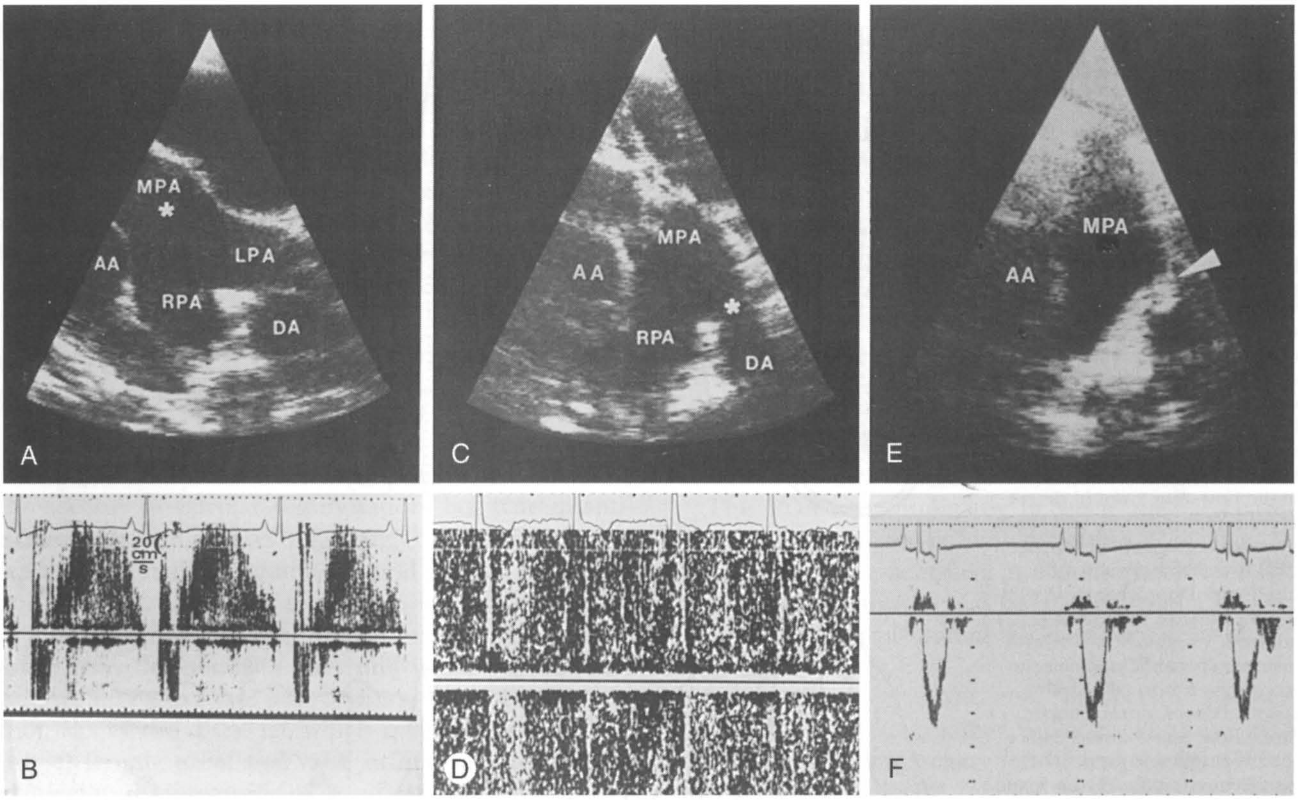


FIGURE 8–16

Two-dimensional (A, C, E) and pulsed-wave Doppler (B, D, F) echoes recorded from the left cranial position in a dog with left-to-right–shunting patent ductus arteriosus. (A) 2-D short-axis view illustrating the main pulmonary artery *(MPA),* right pulmonary artery *(RPA),* left pulmonary artery *(LPA),* descending aorta *(DA),* and ascending aorta *(AA).* (B) Pulsed-wave Doppler trace (sample volume placement indicated by the star) showing retrograde diastolic flow in the MPA. A broad spectral Doppler echo profile appears above the baseline, indicating flow toward the transducer. The spectral display below the baseline shows part of the systolic antegrade flow through the pulmonary artery. (C) 2-D echo short-axis view obtained by rotating the transducer slightly counterclockwise. The communication of the patent ductus arteriosus is evident between the MPA and DA. (D) Pulsed wave Doppler trace recorded with the sample volume positioned approximately at the PDA. Continuous turbulent flow is displayed as an aliased signal and proves patency of the ductus arteriosus. The audio component of the Doppler signal correlates with the sound of the auscultated murmur. (E) Postoperative 2-D short-axis echo image showing the ligated ductus *(arrowhead).* (F) Pulsed-wave Doppler trace with the sample volume positioned in the main pulmonary artery. Note that normal, laminar, antegrade systolic flow is detected. Diastolic flow is absent. The distance between the vertical markers is 20 cm/sec.

VENTRICULAR SEPTAL DEFECT

Most ventricular septal defects (VSDs) are small, high, membranous lesions (Fig. 8–17; see also Figs. 1–3*D,* 24–32*A,* 24–33 and Color Plates 5 and 6). Optimal visualization is usually obtained from the cross-sectional view at the level of the aorta. Alternatively, the right parasternal long-axis view may show the defect and is the best position for Doppler echocardiographic interrogation, since blood flowing through the defect is approximately parallel to the Doppler beam. Rarely, the defect occurs in other areas of the interventricular septum (Fig. 8–17*B*). When a VSD is of adequate size, the lesion may be readily visualized. However, because of inadequate lateral resolution, 2-D echocardiography consistently underestimates the size of a VSD. In small dogs and in cats, actual visualization can be difficult. Doppler echocardiography, and especially color-flow imaging,[87] enhances the sensitivity for the detection of even the smallest lesions.

Determination of peak blood flow velocity through a VSD can be hampered by eccentric jet directions (see Fig. 24–32*A*), which makes detecting the true maximal jet velocity difficult. Also, the Bernoulli equation is best suited for discrete stenosis, and the derived gradient may not actually reflect the ventricular pressure difference. Because of the series effect, flow disturbance (turbulence) from a VSD may pass into the pulmonary artery before relaminarization (subsidence of turbulence) has occurred. Identification of laminar and nonlaminar flow across the cardiac valves is important if pulmonary blood flow (Qp) to systemic

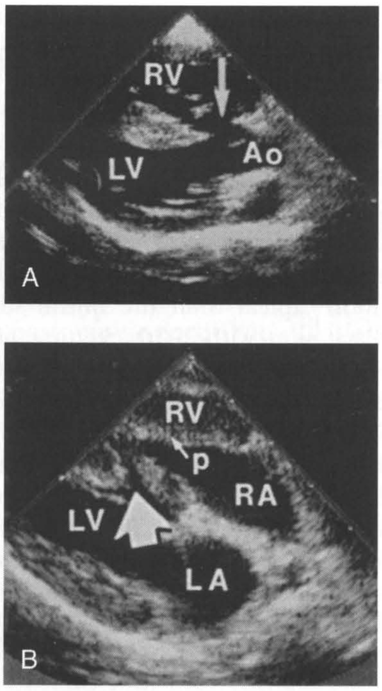


FIGURE 8–17

Two-dimensional echoes of two dogs with ventricular septal defects recorded from the right parasternal transducer location. (A) Long-axis view optimized for the left ventricular outflow tract shows a large basal (membranous) ventricular septal defect *(arrow)*. (B) Long-axis four-chamber view optimizing right and left ventricular inflow tracts. A midventricular (muscular) septal defect is evident. *RA*, right atrium; *RV*, right ventricle; *LA*, left atrium; *LV*, left ventricle; *p*, papillary muscle; *Ao*, aorta.

blood flow (Qs) ratios (Qp:Qs) are to be calculated. This can be estimated with a VSD if the volume (flow velocity integral and cross-sectional area of orifice) for pulmonary flow is measured in the pulmonary artery or mitral valve, and the systemic flow is measured in the aorta.[24, 25]

RESTRICTIVE VSDS. Most VSDs are small, "restrictive" lesions permitting minimal left-to-right shunting. Doppler examination can indicate shunt direction (see Figs. 24–32*A*, 24–38 and Color Plates 5 and 6) and quantify the peak flow velocity across the defect (see Fig. 24–38 and Color Plate 5), allowing an estimation of the instantaneous pressure difference across the defect by the modified Bernoulli equation.[14, 85] High-pressure gradients (e.g., >60 mmHg) indicate a large difference between left and right ventricular pressures. This suggests a small VSD shunting a low blood volume at high velocity across the defect. In these restrictive VSDs there are often no cardiac chamber abnormalities since the shunt fraction is low. Sometimes, prolapse of an aortic (see Fig. 24–33) or tricuspid valve leaflet into the defect may occur, occasionally closing the defect.

NONRESTRICTIVE VSDS. In left-to-right shunting, nonrestrictive VSDs, increased venous return to the left atrium and ventricle causes enlargement of those chambers. Very occasionally, pulmonary edema can result from marked shunting (e.g., >2.5:1 pulmonary-to-systemic flow). If high pulmonary vascular resistance and pulmonary hypertension develop, right ventricular systolic and diastolic pressures increase to systemic levels and reversed (right-to-left) shunting may occur *(Eisenmenger's physiology)*. Thus, very large nonrestrictive VSDs (e.g., tetralogy of Fallot) have only mildly elevated trans-septal pressure gradients, equilibration of blood pressure in both ventricles, and right ventricular hypertrophy.

ATRIAL SEPTAL DEFECT

An atrial septal defect (ASD) can be detected by views that include both atria in the imaging plane. The foramen ovale is covered only by a thin membrane, and the normal atrial septum thins as it approaches the foramen ovale. Thus, echo "dropout" at this point may be misdiagnosed as a defect.

Atrial septal defects are classified according to their position in the septum and their embryogenesis (see Fig. 1–3*B,C*). An *ostium primum* defect is positioned in the lower portion of the septum, contiguous with the atrioventricular valves and membranous interventricular septum (see Fig. 24–26*B* and Color Plate 8). It results from incomplete fusion of the septum primum and endocardial cushions (see Fig. 1–3*C,D*). It is considered a partial form of the common AV canal, which includes cleft and variably fused mitral valve leaflets. When a high interventricular septal defect coexists, a complete *common AV canal* is said to be present. A *sinus venosus* defect is rare and is located high in the interatrial septum, close to the opening of the cranial vena cava (see Fig. 8–3 and Color Plate 7). An *ostium secundum* defect is located in the region of the fossa ovalis (midatrial region) (see Fig. 8–2) because of incomplete development of the septum secundum.

Most ASDs are left-to-right shunting and cause RA and RV dilation. The main pulmonary artery may also be dilated, but the LA is normal or slightly enlarged. With large shunts or with common AV canals, dilation of the left side of the heart develops. Doppler echo examination usually detects (1) transatrial septal flow during systole and diastole that varies with respiration (greatest flows occur during systole but smaller, broader peaks often occur during diastole); (2) increased transpulmonic valve velocity, and often (3) mitral insufficiency. Echocontrast may traverse the defect with right-to-left or bidirectional shunting (see Figs. 8–2, 8–3; see also Fig. 24–26).

When mapping blood flow in the atria, tricuspid regurgitation may be confused with blood flowing across an ASD in some cases. One distinguishing aid is that blood flow velocity across an ASD is usually low

(e.g., in children, a mean velocity of 41 cm/sec),[88] a contrast to the higher velocity usually found with tricuspid insufficiency.[85, 89] Also, flow disturbance with tricuspid regurgitation is purely systolic, beginning after the QRS complex.

The Qp:Qs (shunt) ratio can be determined with an ASD. This is accomplished by using the flow velocity integral and cross-sectional area of the pulmonary artery for Qp, and the mitral or aortic valve for Qs.[24, 25, 85]

ATRIOVENTRICULAR VALVE DYSPLASIA

In multiple echocardiographic views, some or all of the following 2-D echo changes may occur with dysplasia of mitral or tricuspid valves:

1. Adherence of the tricuspid septal leaflet to the interventricular septum,
2. Focal or diffuse AV valvular leaflet thickening or fusion, sometimes resulting in stenosis,
3. Direct insertion of valve leaflets onto papillary muscle,
4. Atrophy or hypertrophy of papillary muscles,
5. Fusion or shortening of chordae tendineae of papillary muscles,
6. Redundant and elongated valve leaflets,
7. Upward displacement of papillary muscles,
8. Apical displacement of the tricuspid valve leaflet hinge points (*Ebstein's malformation*), and
9. Atrial and ventricular dilation.

The four-chamber apical view may provide the best visualization. Doppler echo reveals the presence and direction of regurgitant jets and, often, increased transvalvular filling velocities from the volume overload.

The differentiation between Ebstein's malformation and tricuspid valve dysplasia rests in determining the degree of apical displacement of the tricuspid septal leaflet. Normally the basilar tricuspid valve attachments are more apical than the mitral valve attachments. Displacement without thickening of the valve leaflets downward into the RV is usually defined as Ebstein's anomaly; however, distinct differentiation from tricuspid valve dysplasia may be difficult. Flattening of the interventricular septum occurs because of the overloaded RV. Concurrent ASD or patent foramen ovale may be present with either variation.

Color-flow and spectral Doppler echocardiography usually show marked AV valvular regurgitation (Fig. 8–18; see also Fig. 24–56). The regurgitant jet velocity may not be high[90–93] unless valvular stenosis is present.

AORTIC STENOSIS

Subaortic stenosis (SAS) is the most common form of aortic stenosis (AS), although valvular and supravalvular AS has been reported in the cat and dog.

TWO-DIMENSIONAL ECHOCARDIOGRAPHY. A number of abnormalities can be identified from the right para-

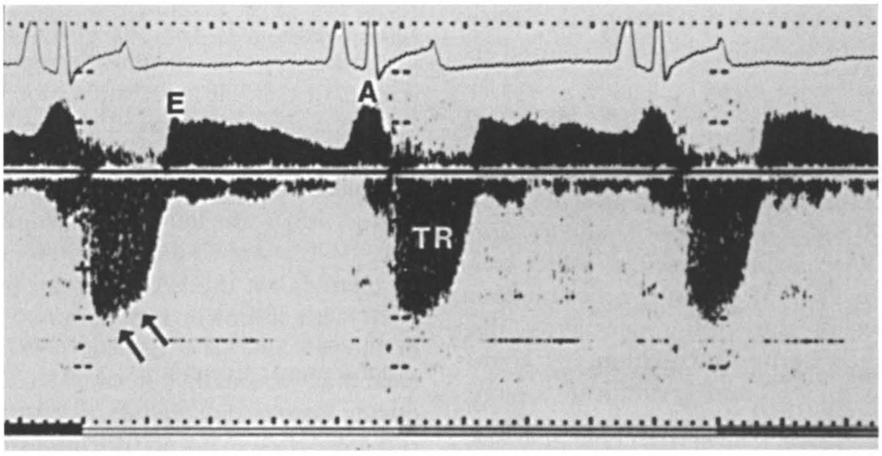


FIGURE 8–18

Continuous-wave Doppler echo recorded across the tricuspid annulus from the apical four-chamber view in a dog with severe tricuspid dysplasia. During right ventricular diastolic filling, flow through the tricuspid valve is depicted as a spectral trace above the baseline (toward the transducer). Diastolic filling is recorded as an early, passive filling phase (E wave), followed by a later filling phase (A wave) resulting from atrial contraction. Here, the A wave is more prominent than usual due to right heart volume overload imposed by the tricuspid regurgitation *(TR)*. During systole, blood regurgitates from the right ventricle into the right atrium (away from the transducer), causing the Doppler trace below the baseline. In late systole, regurgitant velocity is reduced *(arrows)*, reflecting late systolic increase in right atrial pressure (RV-RA pressure difference). The distance between the vertical markers is 1 m/sec.

sternal long- (Fig. 8–19; see also Fig. 24–19) and short-axis (see Fig. 24–13) views in dogs with SAS[94]: (1) concentric left ventricular hypertrophy (unless the condition is mild); (2) LV papillary muscle hypertrophy; (3) a fibrous subaortic band that may protrude or appear muscular, with a wide, fibrous component; (4) hyperechoic areas within the LV myocardium associated with muscle fibrosis or calcification; (5) elevated transmural pressures, resulting in coronary artery blood flow reversal with dilation of the left coronary artery; (5) poststenotic aortic root dilation; (6) mitral valve abnormalities and thickening occasionally if the fibrous band incorporates portions of the anterior mitral valve leaflets; (7) variable LA enlargement; (8) coarse systolic fluttering of the aortic valve if substantial aortic regurgitation is present; mild aortic valve systolic fluttering may be normal or increased with high blood flow; (9) discrete premature aortic valve closure accompanying dynamic left ventricular outflow obstruction; (10) dynamic obstruction to LV outflow from systolic anterior motion when the anterior mitral valve leaflet coapts with the ventricular septal base to encroach on the outflow of blood. Some dogs at rest may not exhibit LV outflow obstruction; disclosure may occur after extrasystolic beats, or provocative testing with isoproterenol or exercise may be necessary for its detection (see Fig. 24–21). Systolic anterior motion is not pathognomonic of subaortic stenosis and may be present in hypertrophic cardiomyopathy, left ventricular hypertrophy, and hypercontractile states.

The severity of the subaortic stenosis can be judged by the degree of myocardial thickening, presence of hyperechoic lesions, and objectively by the pressure gradient across the area of stenosis. Morphologic grades of SAS have been described from necropsy[95]: grade 1—small, slightly raised subvalvular nodules; grade 2—a narrow, thickened subvalvular ridge partially surrounding the LV outflow tract; and grade 3—a complete subvalvular fibrous band or collar surrounding the LV outflow tract, sometimes involving the cranioventral mitral valve leaflet.

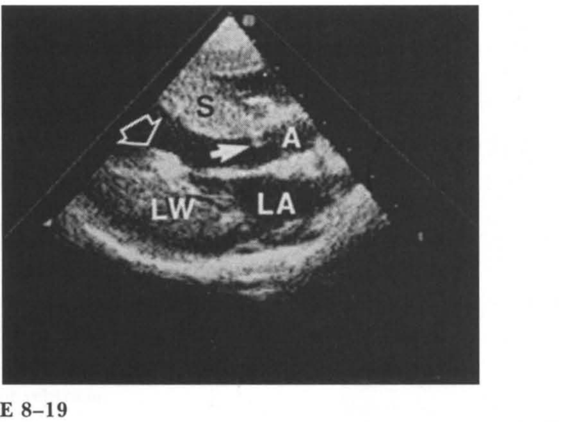


FIGURE 8–19

Two-dimensional echo recorded at the right parasternal transducer location in a dog with congenital subaortic stenosis. The long-axis view is optimized to display the left ventricular outflow tract. There is hypertrophy of the interventricular septum *(S)* and left ventricular posterior wall *(LW)*. A distinct subvalvular fibrous band is present *(arrow)*. A hyperechoic subendocardial region is evident in the papillary muscle *(open arrow)*. *LA*, left atrium; *A*, aorta.

DOPPLER ECHOCARDIOGRAPHY. Doppler examination will demonstrate the maximal systolic pressure gradient (ΔP) from the peak transaortic velocity[41, 96–100] according to the modified Bernoulli equation: ΔP (change in pressure) = $4 \times [\text{velocity}]^2$ (see Fig. 8–4, *Frame 2*; see also Figs. 24–16, 24–20). The maximal velocity is often best determined from the suprasternal, subcostal, or left caudal (apical) locations. In mild cases the only detected abnormality may be increased aortic blood-flow velocity. Color-flow Doppler echocardiography reveals systolic turbulence distal to the obstruction. Mild aortic regurgitation is usually present in dogs with subaortic stenosis. Maximal Doppler pressure gradients of over 125 mmHg are considered severe. By cardiac catheterization, traditional gradients suggesting the level of severity are mild stenosis, gradient of less than 50 mmHg; moderate stenosis, 50 to 75 mmHg; and severe, over 75 mmHg. General anesthesia depresses pressure gradients at least 50 percent.

PULMONIC VALVE STENOSIS

Pulmonic stenosis (PS) most commonly results from pulmonic valve dysplasia, although infundibular, subvalvular, and supravalvular PS have been reported. Subvalvular or valvular PS is a component of tetralogy of Fallot. Short axis-views best visualize these lesions.

TWO-DIMENSIONAL ECHOCARDIOGRAPHY. Characteristic changes (Fig. 8–20; see also Fig. 24–9) include: (1) RV hypertrophy and papillary muscle enlargement, (2) paradoxic ventricular septal motion, (3) muscular narrowing of the RV outflow tract, (4) hyperechoic lesions within the RV myocardium, indicating severe fibrosis or calcification, (5) poststenotic dilatation of the main pulmonary artery, (6) increased echogenicity and thickening of the pulmonary valves, (7) a narrowed pulmonary valve orifice, and (8) variable right atrial enlargement. Concurrent lesions may occur, such as anomalous left main coronary artery, especially in English bulldogs and boxers, and tricuspid valve dysplasia.

DOPPLER ECHOCARDIOGRAPHY. Common findings include turbulence in the pulmonary artery, increased blood velocity across the stenosis, pulmonic insufficiency, and a valvular gradient (see Fig. 8–4, *Frame 1*). Optimal ultrasound beam alignment across the pulmonary valve may be difficult, and the right ventricular outflow tract should be imaged from both the left

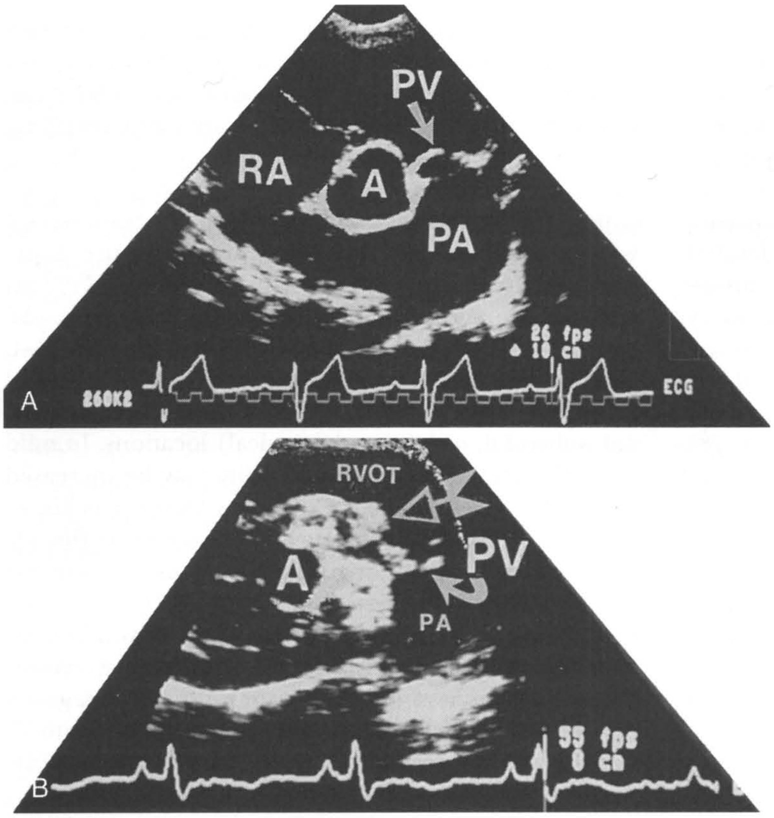


FIGURE 8–20

Two-dimensional echoes recorded at the right parasternal transducer location in two different dogs with pulmonic stenosis. (A) Short-axis view at the level of the aorta shows thickened pulmonary valve *(PV)* leaflets (which had decreased range of motion); narrowed pulmonary valve annulus; and dilated main pulmonary artery *(PA)* (poststenotic dilation). *RA,* right atrium; *A,* aorta. (B) Oblique short-axis view at the level of the aorta shows dysplastic pulmonary valves *(PV)* *(curved arrow)* that are greatly thickened, and subvalvular (infundibular) hypertrophy *(arrow)*. *PA,* main pulmonary artery; *RVOT,* right ventricular outflow tract; *A,* ascending aorta.

cranial and right parasternal locations to detect the maximal velocity. The pressure gradient across the stenotic pulmonic valve may then be determined ($\Delta P = 4 \times [\text{velocity}]^2$).[101] Dogs with a gradient of less than 50 mmHg are considered to have mild PS, whereas severe PS is indicated in dogs with gradients of greater than 125 mmHg. The best candidates for balloon valvuloplasty are dogs with gradients of greater than 75 mmHg that do not have severe structural and functional alteration and have purely valvular stenosis.

TETRALOGY OF FALLOT

Two-dimensional echocardiography is used to identify components of this cyanotic congenital cardiac anomaly. The pulmonary trunk and pulmonic valves should be examined carefully at their sites of origin to differentiate tetralogy of Fallot from truncus arteriosus or pulmonic atresia.

TWO-DIMENSIONAL ECHOCARDIOGRAPHY. Features (see Fig. 24–52) include (1) a large, subaortic ventricular septal defect, (2) a dextropositioned (overriding) aorta, (3) right ventricular outflow obstruction (pulmonic stenosis), and (4) secondary right ventricular hypertrophy. The aorta may be enlarged owing to increased flow through the VSD. Left atrial and ventricular size are generally small. Ventricular septal hypertrophy and paradoxic or flattened septal motion are present. Pulmonary atresia and hypoplasia of the supraventricular crest may be present. Echocontrast studies document right-to-left shunting through the VSD.

DOPPLER ECHOCARDIOGRAPHY. Doppler examination reveals right-to-left shunting across the VSD into the aorta and severe pulmonic stenosis. Pulmonary hypertension as a potential cause of right-to-left shunting must be ruled out.

ECHOCARDIOGRAPHIC EVALUATION OF ACQUIRED DISEASE

CHRONIC ACQUIRED ATRIOVENTRICULAR (AV) VALVE DISEASE

Atrioventricular valve insufficiency results from chronic acquired valve disease (endocardiosis, myxomatous degeneration). It is easily evaluated by 2-D and Doppler echocardiography, but the cost-benefit value of these studies in uncomplicated cases is unproved.

TWO-DIMENSIONAL ECHOCARDIOGRAPHY. Right parasternal long- and short-axis views are well suited for 2-D evaluation. Atrioventricular valve leaflets are thickened and nodular (Fig. 8–21; see also Fig. 8–12) and may protrude into the atria during systole. Regurgitation severity can be indirectly estimated by the degree of ventricular and atrial enlargement, which may be pronounced in advanced cases.

When mitral insufficiency is present, the percent fractional shortening (%FS) provides only an approximation of systolic function because preload and afterload markedly affect this index. Since left atrial pressures are lower than systemic arterial pressures, it is easier for the LV in cases of mitral insufficiency to eject blood into the LA than into the aorta. With mild mitral insufficiency and low regurgitant fraction, the %FS will be normal. However, as the regurgitant fraction increases while myocardial function is preserved, the %FS also increases. That is, the LV "unloads" blood more readily, albeit retrogradely, into the LA, such that the %FS is elevated, even when early myocardial failure is present. During diastolic ventricular filling, ventricular septal motion is exaggerated toward the RV. Enhanced ventricular unloading and increased preload contribute to a supranormal %FS value (Fig. 8–22*A*). If myocardial failure develops, the %FS declines, and values ultimately may be recorded in the normal range (Fig. 8–22*B*). Myocardial failure is generally uncommon with acquired canine mitral regurgitation.[67]

The E-point septal separation (EPSS) is an indicator of inotropic state as well as chamber diameter and is usually normal unless significant and chronic mitral regurgitation is present. This measurement highly depends on beam orientation.

DOPPLER ECHOCARDIOGRAPHY. Doppler echocardiography can identify and semiquantify valvular insufficiency (Color Plate 10). Spectral Doppler echocardiography may show a high peak regurgitant velocity in mitral regurgitation (5 to 6 m/sec) but relatively lower velocities (<2 m/sec) in tricuspid regurgitation (high-velocity tricuspid regurgitation [>4 m/sec] usually suggests pulmonary hypertension). Insignificant pulmonic and aortic insufficiency (<2 m/sec) are commonly present in some affected dogs. Assessment of the regurgitant jet's size (length and area) depends not only on the amount of regurgitation but also on the characteristics of the receiving chamber. Limitations in quantifying AV valve insufficiency have been reviewed.[82, 102]

MYOCARDIAL DISEASES

Echocardiography has greatly improved characterization of cardiomyopathies. Dilated, hypertrophic,

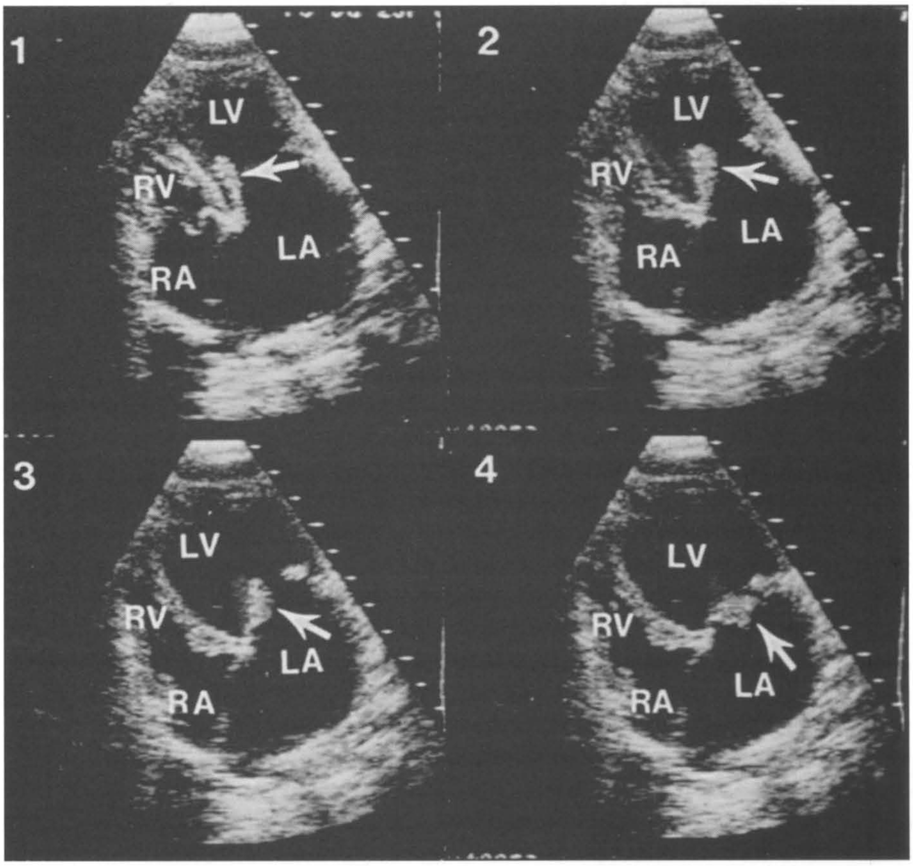


FIGURE 8–21

Two-dimensional echo of a poodle with chronic acquired valve disease (endocardiosis) and severe mitral regurgitation recorded at the left apical (caudal) transducer location. Sequential frames in this apical four-chamber view demonstrate mitral valve motion and severely thickened leaflets. During early (*Frames 1* and *2*) and late (*Frame 3*) diastole, the anterior mitral valve leaflet (*arrow*) moves normally, but the posterior leaflet is relatively immobile. In *Frame 4*, the thickened leaflets protrude into the left atrium (*LA*). The LA and left ventricle (*LV*) are dilated from volume overload. *RA*, right atrium; *RV*, right ventricle.

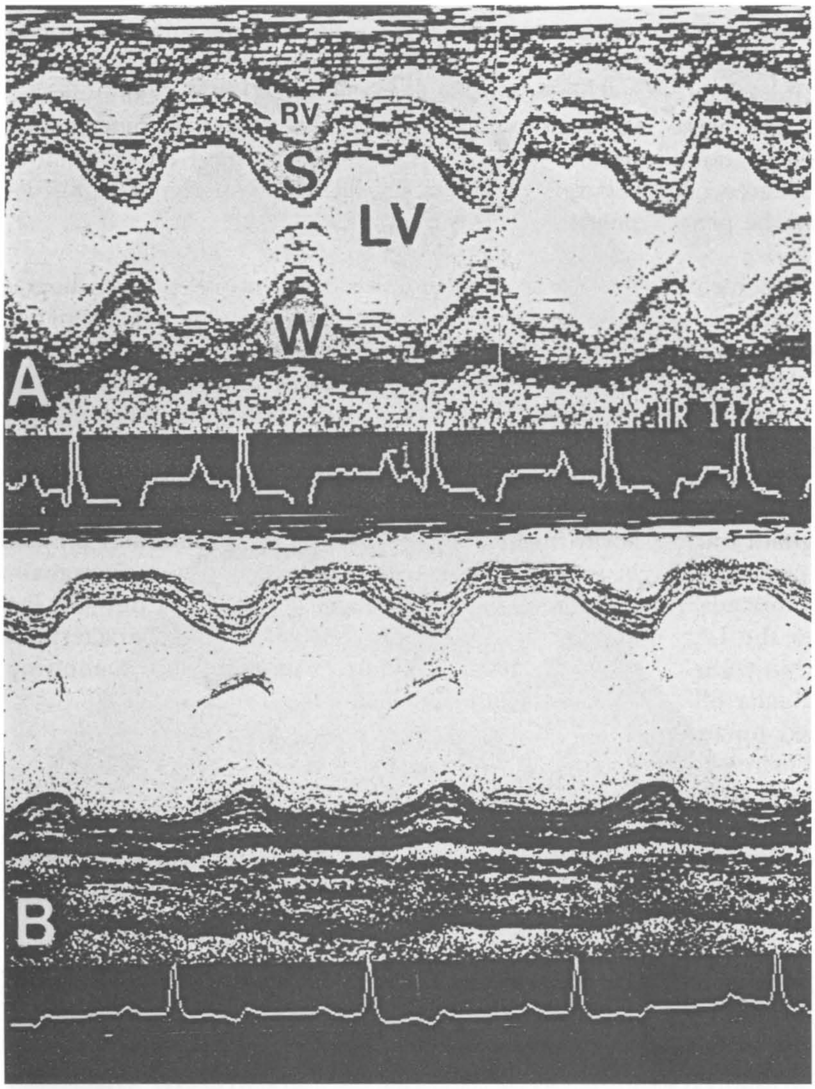


FIGURE 8–22

M-mode echoes of two dogs with chronic acquired valve disease (endocardiosis) recorded at the ventricular level just below the mitral valve. (A) Nine-year-old poodle with asymptomatic compensated mitral insufficiency. Ventricular septal and LV free wall motion are hyperdynamic; fractional shortening is elevated (55%). (B) Fifteen-year-old Lhasa Apso with decompensated mitral and tricuspid regurgitation. Motion of the ventricular septum is exaggerated relative to the hypokinetic LV free wall. Whereas the fractional shortening (35%) may be within the low-normal range for some healthy, unaffected dogs, it is too low for a dog with severe mitral regurgitation and indicates left ventricular myocardial failure. Left ventricular end-systolic and end-diastolic dimensions are also increased. *RV*, right ventricular chamber; *S*, interventricular septum; *LV*, left ventricular chamber; *W*, left ventricular wall.

and restrictive cardiomyopathies can be readily differentiated.[58, 62, 66, 103–109]

DILATED (CONGESTIVE) CARDIOMYOPATHY

TWO-DIMENSIONAL ECHOCARDIOGRAPHY. The following echocardiographic findings may be detected[81] (see Figs. 27–6, 28–20): (1) dilated left and right ventricles, (2) dilated left and right atria, (3) hypokinetic and paradoxic septal motion, (4) severely reduced fractional shortening and velocity of circumferential fiber shortening, (5) reduced left ventricular free wall amplitude, (6) normal-to-thin myocardial wall thickness, (7) increased E-point septal separation, (8) decreased mitral valve excursions, (9) abnormal delayed closure of the mitral valve, resulting in a visible hump ("B shoulder"), (10) dilated left ventricular outflow tract, (11) decreased aortic root amplitude and diameter, (12) abnormal systolic time intervals (decreased LV ejection time and prolonged pre-ejection period), (13) spontaneous echo contrast formation suggesting blood stasis, (14) LA or LV thrombi in cats, and (15) pericardial, pleural, or abdominal effusion. Canine dilated cardiomyopathy is frequently associated with atrial fibrillation.[105]

DOPPLER ECHOCARDIOGRAPHY. Doppler echocardiographic studies can provide additional information about myocardial function.[102, 106] The velocity of blood flow across the cardiac valves is reduced. Hemodynamic determinations are most frequently quantified from the aortic flow velocity curves. Diastolic function may also be abnormal.

HYPERTROPHIC CARDIOMYOPATHY

Echocardiography is a highly sensitive test of left ventricular hypertrophy.[58, 62, 104] Feline hypertrophic cardiomyopathy (HCM) is morphologically heterogeneous.[66, 104] In feline hyperthyroidism, LV hypertrophy, LA and RA enlargement, increased %FS and indices indicating a hypercontractile state are com-

mon.[107] These changes are often reversible when euthyroidism is re-established and maintained.

TWO-DIMENSIONAL ECHOCARDIOGRAPHY. Characteristic 2-D echo findings[66] (see Figs. 28–3, 28–5, 28–7, 28–14) include (1) LV hypertrophy (LV free wall or ventricular septum >6 mm at end-diastole; wall thickening is most commonly diffuse, involving the ventricular septum and free wall). Less frequently, it may be segmental and confined to the anterior ventricular septum; (2) moderately to severely enlarged LA and left auricle, often accompanied by RA enlargement of lesser severity; (3) left ventricular internal dimensions usually normal at end-diastole but decreased at end-systole; (4) dynamic LV outflow tract obstruction associated with systolic anterior motion (SAM) of the anterior mitral valve, and corresponding midaortic valve closure; the anterior mitral valve leaflet is usually thickened and endocardial plaque is present in the basilar ventricular septum, corresponding to the point of SAM-septal contact; (5) fractional shortening usually normal but may be increased; (6) possible LA or LV thrombi (see Fig. 28–14); and (7) pericardial or pleural effusion in some cats. Endomyocardial fibrosis may sometimes cause increased echogenicity. Canine HCM is rare and not well described.

DOPPLER ECHOCARDIOGRAPHY. Doppler studies reveal mild mitral insufficiency in most cats. When dynamic LV outflow tract obstruction is present, regurgitant jets originate at the site of SAM-septal contact; they can be of high velocity (>4 m/sec); and they have an eccentric orientation, often directed toward the caudal LA border (see Figs. 28–4, 28–5). Cats with the nonobstructive form of HCM have mild mitral regurgitant jets of lower velocities, originating from the mitral valve commissures. With the obstructive form of HCM, forward aortic velocities are increased (typically, 2 to 4.5 m/sec), with a characteristic late peaking contour and corresponding midaortic valve closure on M-mode echo.[66] In addition, diastolic dysfunction may be associated with changes in transmitral filling patterns. Characteristic LV relaxation abnormalities are reflected by reversal of early and late filling waves (E:A reversal). Here the Doppler echo A wave (following atrial contraction in late diastole) is exaggerated relative to the early diastolic inflow velocity (E wave), as the atria contract to fill the stiff, noncompliant left ventricle (see Fig. 28–2). Many factors influence the interpretation of Doppler echo patterns in addition to diastolic dysfunction.[72]

RESTRICTIVE CARDIOMYOPATHY

This feline myocardial disorder is heterogeneous and poorly defined. Echo characteristics include (1) relatively normal LV chamber and wall dimensions, (2) normal or nearly normal systolic function, (3) severe LA enlargement in the absence of significant left-sided heart volume overload, (4) moderate-to-severe RA enlargement, RV enlargement, and variable RV hypertrophy, (5) LA or LV thromboemboli, and (6) variable pleural or pericardial effusion. Doppler studies may disclose mild mitral or tricuspid regurgitation. Some affected cats have a "classic" Doppler mitral filling pattern characterized by a high E wave and very-low-velocity A wave, or relaxation abnormalities (E:A reversal).[109, 110]

IDIOPATHIC ENDOMYOCARDIAL SCARRING

This condition is characterized by endomyocardial fibrosis with large endocardial plaque. Echocardiographic characteristics (see Fig. 28–16) include (1) LV hypertrophy and severe LV enlargement, (2) variable RA and RV enlargement and hypertrophy, (3) severe mid-LV endocardial scar, usually bridging the LV free wall and ventricular septum, and occasionally obliterating the apical chamber, (4) LA or LV thromboemboli, and (5) variable pericardial and pleural effusion. Doppler studies disclose mild-to-moderate mitral or tricuspid regurgitation and turbulence in the region of the endocardial scar, often with midventricular gradients.[110, 111]

BACTERIAL ENDOCARDITIS

Vegetative endocarditis often can be detected by echocardiography (Fig. 8–23; see also Figs. 26–4, 26–5).[112, 113] The mitral and aortic valves are most frequently involved. Characteristic findings include (1) thickened, shaggy valve leaflets, often with pedunculated, mobile masses, (2) secondary left-sided heart changes due to severe volume overload (e.g., LA and LV enlargement, hyperdynamic LV septal and posterior wall motion), and (3) diastolic flutter of the anterior mitral valve leaflet when aortic regurgitation (from aortic valve vegetations) strikes this mitral leaflet (see Fig. 8–12). Vegetative valvular lesions may calcify, become hyperechoic, and cast *acoustic shadows* (i.e., loss or diminished intensity of gray in a structure located directly behind another highly reflective object). Even if vegetative lesions are not observed, this diagnosis cannot be excluded since small lesions may be below the resolving capability of 2-D echocardiography. Diagnosis is aided by clinical findings and Doppler echo evidence of associated valvular insufficiency. Preexisting valvular disease (chronic myxomatous change, endocardiosis) may hamper recognition of vegetations or simulate lesions. Myocardial abscesses may occur and appear as hypoechoic areas.

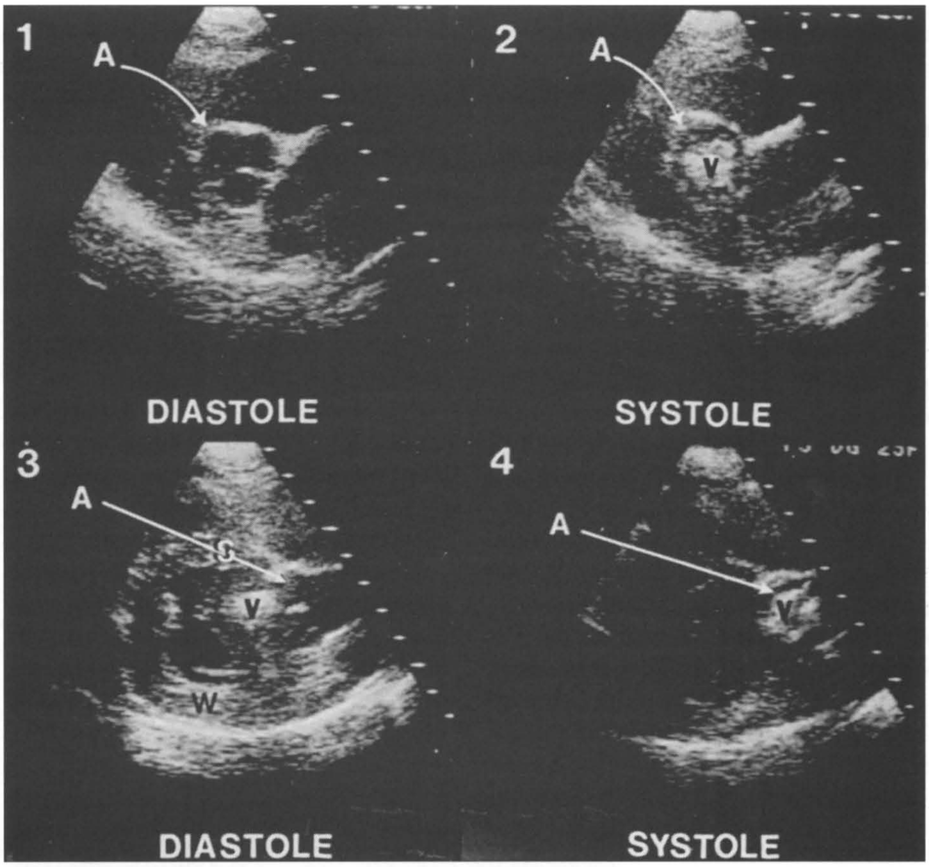


FIGURE 8–23

Two-dimensional echoes recorded from the right parasternal transducer location from a 9-year-old English setter with syncope. *Frames 1* and *2:* Short-axis views at the aortic valve level. During diastole *(Frame 1),* aortic cusps are visible. During systole *(Frame 2)* a large, hyperechoic, vegetative mass is seen to occupy the aortic orifice. *Frames 3* and *4:* Slightly obliqued long-axis views to accentuate the LV outflow tract and aortic root. During diastole *(Frame 3)* the hyperechoic vegetative mass is situated in the LV outflow tract. Notice the darkened area of echo dropout in the LV posterior wall *(W)* directly below the vegetation. This *acoustic shadow* is caused by the vegetative mass blocking ultrasound transmission. During systole *(Frame 4),* the mass enters the aortic root. *S,* ventricular septum; *A,* aortic root; *v,* vegetative mass.

PERICARDIAL AND PLEURAL EFFUSIONS

Echocardiography is sensitive for diagnosing pericardial and pleural effusions (Figs. 8–24 to 8–27; see also Figs. 29–15, 29–17).[114–116]

PERICARDIAL EFFUSION. Most pericardial disorders are associated with pericardial effusion or cause diffuse pericardial involvement. Effusion is identified by a relatively anechoic (black) or hypoechoic (dark) area (i.e., echo-free space) between the epicardium and pericardium; it occasionally contains fibrous bands, thrombi, focal tumor implants, or loculated effusion. Careful and extensive examination using multiple imaging planes and positions is indicated to search for etiology.

Pericardial effusion is indicated in short-axis views by (1) separation of visceral and parietal pericardial surfaces by an echo-free space (Fig. 8–25, *Frames 2,4*), and (2) swinging of the entire heart within the pericardial space with severe effusions. In the right parasternal long-axis view, pericardial effusion collects initially behind the posterior LV wall just distal to the atrioventricular groove. It is most abundant at the cardiac apex, decreases toward the heart base, and is virtually absent behind the left atrium (prevented by venous pericardial attachments) (Figs. 8–24, *Frame 3,* 8–25; see also Figs. 28–16, 29–17).

CARDIAC TAMPONADE. Rapid accumulation of a small amount of intrapericardial fluid, or chronic accumulation of a large volume, can raise intrapericardial pressure and impair diastolic filling. *Tamponade* describes the spectrum of cardiac abnormalities whose echocardiographic features (Fig. 8–24, *Frame 4*) include (1) pericardial effusion, usually moderate-to-severe, (2) diastolic inversion (collapse) of the right atrial or ventricular walls, and (3) generalized compression of the right side of the heart at very high pressures. Doppler echocardiography may record exaggerated respiratory

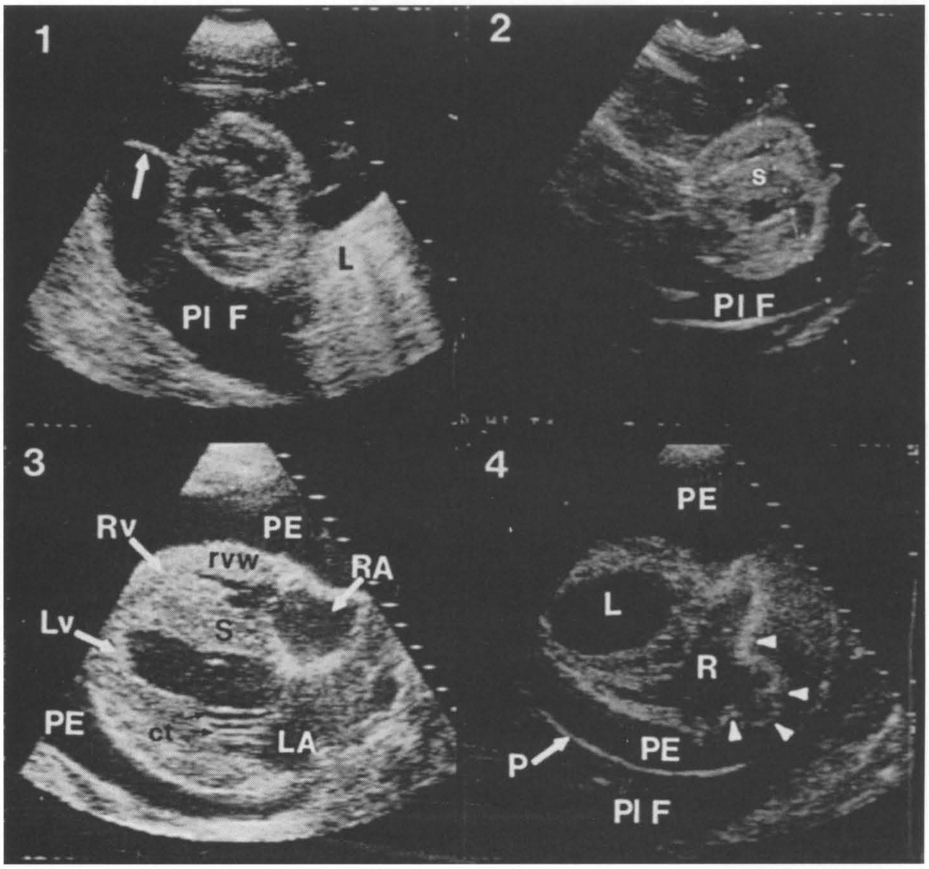


FIGURE 8–24

Two-dimensional echoes demonstrating pleural and pericardial effusions recorded from the right parasternal location. *Frame 1:* Short-axis view of the left and right ventricles at the papillary level, recorded from a cat with pleural fluid *(Pl F).* The appearance of the pericardiodiaphragmatic ligament *(arrow)* and lung *(L)* indicate that the effusion is pleural rather than pericardial. *Frame 2:* Similar view recorded during systole of another cat with pleural fluid. The dotted line is the M-mode cursor. *S,* ventricular septum. *Frame 3:* Right parasternal long-axis four-chamber view from a Great Dane with pericardial effusion *(PE).* Notice that the effusion does not traverse behind the whole left atrium *(LA)* but ends slightly distal to the atrioventricular groove. *RA,* right atrium; *Rv,* right ventricle; *rvw,* right ventricular wall; *Lv,* left ventricle; *S,* ventricular septum; *ct,* chordae tendineae. *Frame 4:* A German shepherd with pericardial and pleural effusion that outlines the pericardium *(P)* as a circular sac around the heart. The left ventricular epicardium and parietal pericardium are separated by a sonolucent (''echo-free'') space caused by pericardial effusion *(PE).* The contour of the right ventricle is indicated *(arrowheads),* outlined by pericardial effusion and pleural fluid *(Pl F).* Notice that the right ventricle *(R)* collapses inward during this diastolic frame because of cardiac tamponade. *L,* left heart.

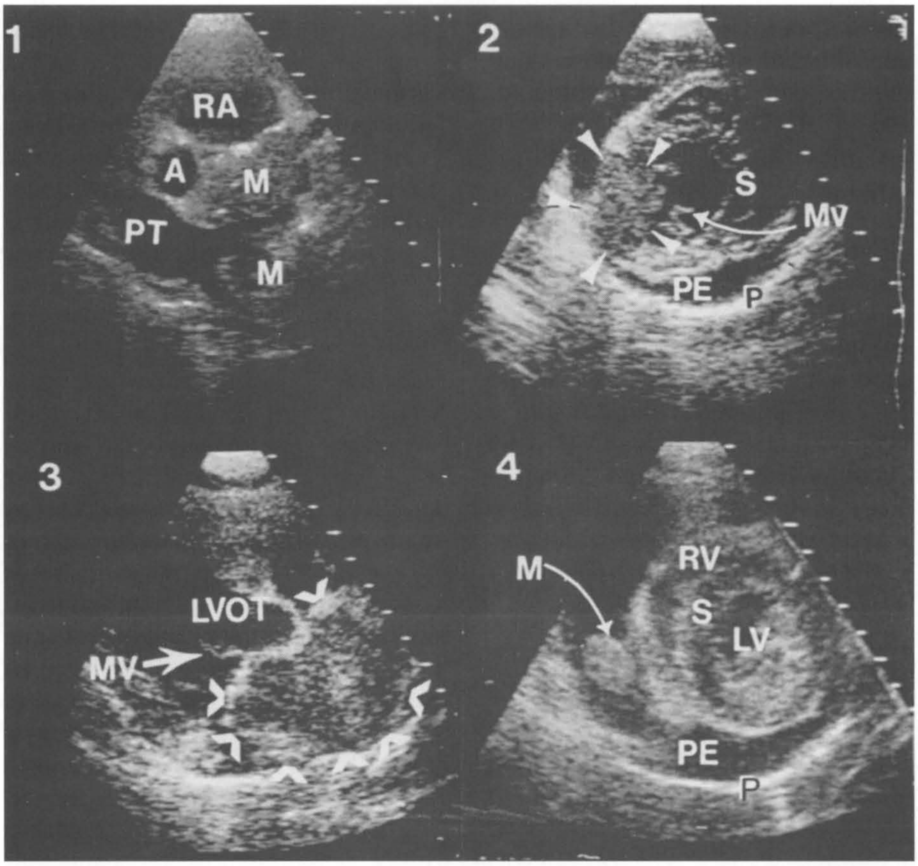


FIGURE 8–25

Two-dimensional echoes of dogs with various heart-base tumors, recorded from the right parasternal transducer position. *Frame 1:* Short-axis view at the aortic level of a mixed-breed dog. A mass *(M)* surrounds the aorta *(A)* and the right and left pulmonary arteries. *RA,* right atrium; *PT,* pulmonary trunk. *Frame 2:* Short-axis view at the atrioventricular level from a miniature poodle with a chemodectoma. A mass *(arrowheads)* that protrudes into the left atrium is of different echogenicity (appearing hypoechogenic, or "moth-eaten") relative to the myocardium. *PE,* pericardial effusion; *S,* interventricular septum; *Mv,* mitral valve; *P,* pericardium. *Frame 3:* Oblique, long-axis view of the LV outflow and inflow tract recorded from an English bulldog with a chemodectoma. The tumor *(arrowheads)* is large and encroaches on the left atrium. *LVOT,* left ventricular outflow tract; *MV,* mitral valve. *Frame 4:* Short-axis view at the papillary muscle level, recorded from a 10-year-old golden retriever. A mass *(M)* is apparent within the pericardial effusion *(PE)* adjacent to the right ventricular wall *(RV).* Right atrial hemangiosarcoma was found at surgery. *S,* ventricular septum; *LV,* left ventricle; *P,* pericardium.

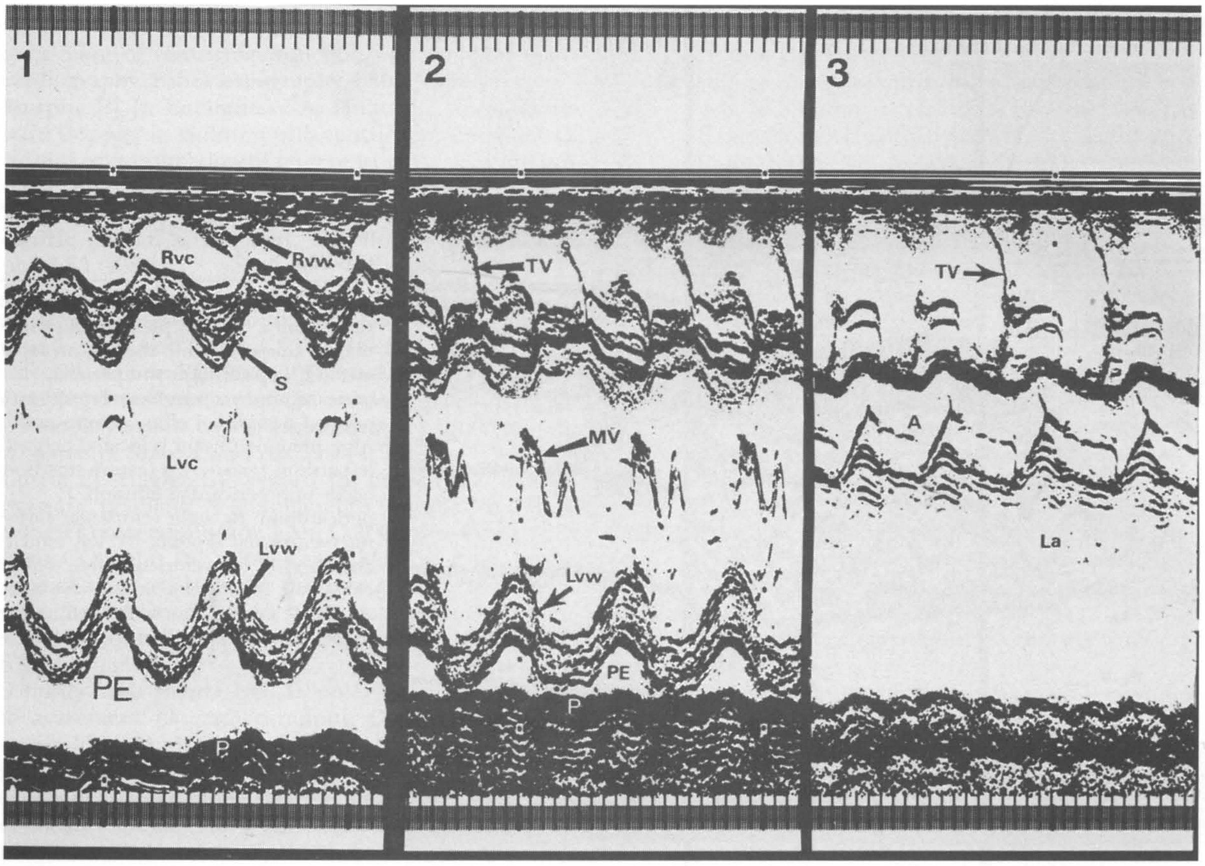


FIGURE 8–26

M-mode echo recordings at three standard views from a dog with mitral and tricuspid insufficiency and pericardial effusion. *Frames 1* and *2:* Pericardial effusion *(PE)* is indicated by a sonolucent, echo-free space between the epicardium and parietal pericardium *(P)*. Pericardial effusion is characteristically most prominent at the cardiac apex, least evident at the base, and is mostly absent behind the left atrium as in *Frame 3* (compare with Fig. 8–27). *Rvw,* right ventricular wall; *Rvc,* right ventricular chamber; *S,* interventricular septum; *Lvc,* left ventricular chamber; *Lvw,* left ventricular free wall; *TV,* tricuspid valve; *MV,* anterior mitral valve leaflet; *A,* aortic root containing aortic valves; *La,* left atrium.

variation of cardiac blood flow and decreased transvalvular flows, especially during inspiration.

PLEURAL EFFUSION. Pleural effusion (Figs. 8–24, *Frames 1,2,4,* 8–27) must be carefully differentiated from pericardial effusion (Figs. 8–24, *Frames 3,4,* 8–25, 8–26). Pleural effusion is detected behind the left atrium (Fig. 8–27), whereas pericardial effusion is minimal or absent there (Fig. 8–26). With pleural effusion, delineation of collapsed lung lobes, the pericardiodiaphragmatic ligament (caudal mediastinum), and cranial mediastinum is possible, but not that of pericardial fluid.

Pericardial and pleural fluid may be present concomitantly. In these cases the pericardium is clearly outlined (Fig. 8–24, *Frame 4*).

INTRACARDIAC AND EXTRACARDIAC MASSES

Two-dimensional echocardiography is very useful to identify intracardiac and extracardiac masses.[117] Diagnostic accuracy is enhanced when cardiac imaging incorporates multiple tomographic views.

Heartworms within the right side of the heart or pulmonary artery can be seen as fine irregular, linear echoes or as a large, irregular dense mass when the worms are incorporated into a thrombus (see Figs. 30–9; 31–5).[117] Echocardiographic changes associated with heartworm disease include (1) RV and RA enlargement, (2) flattened or paradoxic ventricular septal motion, (3) reduced LV and LA chamber dimensions, (4) pulmonary artery enlargement, and (5) pleural or pericardial effusion.

Intracardiac thrombi occur rarely in dogs but are common in the left atrium and ventricle of cats with myocardial disease (see Fig. 28–14). When myocardial failure or left atrial or ventricular enlargement is severe, blood stasis may result in spontaneous echo contrast. This appears as swirling, tiny white or gray echoes within the affected chamber and is often associated with mural thrombi (see Fig. 28–14).

Neoplasia (e.g., chemodectoma, hemangiosarcoma,

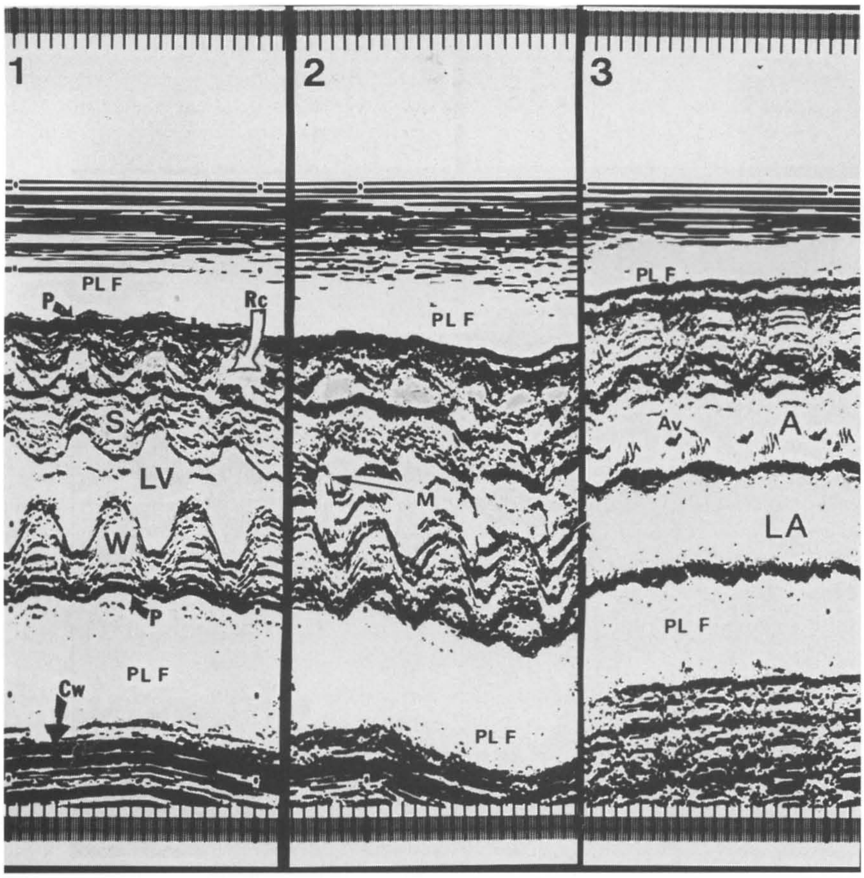


FIGURE 8–27

M-mode echo recordings at three standard views from a cat with pleural effusion. Note that in *Frames 1* and *2*, there is no separation of the LV epicardium and parietal pericardium by a sonolucent space, as would occur if pericardial effusion were present. Also, pleural effusion is located behind the left atrium *(Frame 3)*, a feature that does not occur with pericardial effusion. *P*, pericardium; *Rc*, right ventricular cavity; *S*, interventricular septum; *LV*, left ventricular chamber; *W*, left ventricular free wall; *Cw*, chest wall; *M*, anterior mitral valve leaflet; *Av*, aortic valve; *A*, aorta, *LA*, left atrium; *Pl F*, pleural fluid.

ectopic thyroid adenocarcinoma, metastatic tumors) can be identified best with 2-D echocardiography[118] (Fig. 8–25; see also Figs. 29–18, 29–19). The transducer often must be positioned in a craniodorsal location to image the heart base. Multiple imaging and transducer locations will assure optimal diagnostic accuracy. A mass involving only the RA is more likely to be a hemangiosarcoma than a chemodectoma. Usually, hemangiosarcoma is more likely to have hypoechoic or anechoic areas than is chemodectoma. Most feline intramural masses are lymphosarcoma.

REFERENCES

1. Weyman AD (ed). Principles and Practice of Echocardiography. 2nd ed. Philadelphia, Lea & Febiger, 1994, pp 3, 218, 302
1a. Parrish DL, Grayburn PA. Use of echocardiography in patients with congestive heart failure. Cardiol Rev 6:203, 1998
2. Wells PNT. Biomedical Ultrasonics. New York, Academic Press, 1977
3. Feigenbaum H. Echocardiography. 4th ed. Philadelphia, Lea & Febiger, 1986
4. Picard MH. M-mode echocardiography: Principles and examination techniques. *In* Weyman AD (ed): Principles and Practice of Echocardiography. Philadelphia, Lea & Febiger, 1994, pp 282, 584
5. Seward JB, Khandheria BK, Oh JK, et al. Biplanar transesophageal echocardiography: Anatomic correlations, implementation, and clinical applications. Mayo Clin Proc 63:649, 1988
6. Khandheria BK, Oh J. Transesophageal echocardiography: Technique, anatomic correlations, implementation, and clinical applications. Mayo Clin Proc 63:649, 1988
7. Omoto R, Kyo S, Matsumura M, et al. New direction of biplane transesophageal echocardiography with special emphasis on real-time biplane imaging and matrix phase-array biplane transducer. Echocardiography 7:691, 1990
8. Loyer C, Thomas WP. Transesophageal echocardiography in the dog: Technique, anatomy, and imaging planes. Vet Radiol Ultrasound 36:212, 1995
9. Kienle RD, Thomas WP, Rishniw M. Biplane transesophageal echocardiography in the cat: Technique, anatomy, and image quality. J Vet Intern Med 19:200, 1995
10. Gopal AS, Keller AM, Shen Z, et al. Three-dimensional echocardiography: In vitro and in vivo validation of left ventricular mass and comparison with conventional echocardiographic methods. J Am Coll Cardiol 24:504, 1994
10a. Yao J, Masani ND, Cao Q-L, et al. Clinical application of transthoracic volume-rendered three-dimensional echocardiography in the assessment of mitral regurgitation. Am J Cardiol 82:189, 1998
11. Stevenson JG, Kawabori I. Noninvasive determination of pressure gradients in children: Two methods employing pulsed Doppler echocardiography. J Am Coll Cardiol 3:179, 1984
12. Goldberg SJ, Allen HD, Marx GR, et al. Doppler Echocardiography. Philadelphia, Lea & Febiger, 1985

13. Snider AR. Prediction of intracardiac pressures and assessment of ventricular function with Doppler echocardiography. Echocardiography 4:305, 1987
14. Murphy DJ Jr, Ludomirsky A, Huhta JC. Continuous-wave Doppler in children with ventricular septal defect: Noninvasive estimation of interventricular pressure gradient. Am J Cardiol 57:428, 1986
15. Talano JV. Doppler echocardiography in assessing intracardiac pressures, function, and flow. Echocardiography 3:83, 1986
16. Berger A, Berdoff RL, Gallerstein PE, et al. Evaluation of aortic stenosis by continuous wave Doppler ultrasound. J Am Coll Cardiol 3:150, 1984
17. Fyfe DA, Currie PJ, Seward JB, et al. Continuous wave Doppler determination of the pressure gradient across pulmonary artery bands: Hemodynamic correlation in 20 patients. Mayo Clin Proc 59:744, 1984
18. Currie PJ, Hagler DJ, Seward JB, et al. Instantaneous pressure gradient: A simultaneous Doppler and dual catheter correlative study. J Am Coll Cardiol 7:800, 1986
19. Lima CO, Sahn DJ, Valdes-Cruz LM, et al. Noninvasive prediction of transvalvular pressure gradient in patients with pulmonary stenosis by quantitative two-dimensional echocardiographic Doppler studies. Circulation 67:866, 1983
20. Schuster AH, Nanda NC. Doppler echocardiographic measurement of cardiac output: Comparison with a non-golden standard. Am J Cardiol 53:257, 1984
21. Meijboom EJ, Rijsterborgh H, Bot H, et al. Limits of reproducibility of blood flow measurements by Doppler echocardiography. Am J Cardiol 59:133, 1987
22. Meijboom E, Horowitz S, Valdes-Cruz L, et al. A Doppler echocardiographic method for calculating volume flow across the tricuspid valve: Correlative laboratory and clinical studies. Circulation 71:551, 1985
23. Valdes-Cruz LM, Horowitz S, Mesel E, et al. A pulsed Doppler echocardiographic method for calculating pulmonary and systemic blood flow in atrial level shunts: Validation studies in animals and initial human experience. Circulation 69:80, 1984
24. Barron JV, Sahn DJ, Valdes-Cruz LM, et al. Clinical utility of two-dimensional Doppler echocardiographic techniques for estimating pulmonary to systemic blood flow ratios in children with left to right shunting atrial septal defect, ventricular septal defect, or patent ductus arteriosus. J Am Coll Cardiol 3:169, 1984
25. Valdes-Cruz LM, Horowitz S, Mesel E, et al. A pulsed Doppler echocardiographic method for calculation of pulmonary and systemic flow: Accuracy in a canine model with ventricular septal defect. Circulation 68:597, 1983
26. Kosturakis D, Allen HD, Goldberg SJ, et al. Noninvasive quantification of stenotic semilunar valve areas by Doppler echocardiography. J Am Coll Cardiol 3:1256, 1984
27. Richards KL, Cannon SR, Miller JF, et al. Calculation of aortic valve area by Doppler echocardiography: A direct application of the continuity equation. Circulation 73:964, 1986
28. Richards KL. Doppler echocardiographic quantification of stenotic valvular lesions. Echocardiography 4:289, 1987
29. Gura GM Jr. Video Atlas of Two-Dimensional Color Flow Doppler Echocardiography. Boston, Little, Brown, 1989
30. Enriquez-Sarano M, Tajik AJ, Bailey KR, et al. Color flow imaging compared with quantitative Doppler assessment of severity of mitral regurgitation: Influence of eccentricity of jet and mechanism of regurgitation. J Am Coll Cardiol 21:1211, 1993
31. Danford DA. Basic principles and technical considerations. *In* Kudomirsky A, Huhta JC (eds): Color Doppler of Congenital Heart Disease in the Child and Adult. Mount Kisco, NY, Futura Publishing Company, 1987, p 1
32. Kisslo J, Adams DB, Belkin RN. Doppler Color Flow Imaging. New York, Churchill Livingstone, 1988
33. Gessert JM, Moore GW. Color flow imaging display modes and data acquisition parameters. Echocardiography 4:375, 1988
34. Kienle RD, Thomas WP. Echocardiography. *In* Nyland TG, Mattoon JS (eds): Veterinary Diagnostic Echocardiography. Philadelphia, WB Saunders, 1995, p 198
35. Thomas WP, Gaber CE, Jacobs GJ, et al. Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. J Vet Intern Med 7:247, 1993
36. Darke PGG, Bonagura JD, Miller M. Transducer orientation for Doppler echocardiography in dogs. J Small Anim Pract 34:2, 1993
37. DeMadron E, Bonagura JD, Herring DS. Two-dimensional echocardiography in the normal cat. Vet Radiol 26:149, 1985
38. O'Grady MR, Bonagura JD, Powers JD, et al. Quantitative cross-sectional echocardiography in the normal dog. Vet Pathol 27:34, 1986
39. Thomas WP. Two dimensional real time echocardiography in the dog. Vet Radiol 25:50, 1984
40. Sahn DJ, Anderson F. An Atlas for Echocardiographers; Two-Dimensional Anatomy of the Heart. New York, John Wiley and Sons, 1982
41. Lehmkuhl LB, Bonagura JD. Comparison of transducer placement sites for Doppler echocardiography in dogs with subaortic stenosis. Am J Vet Res 55:192, 1994
42. Sahn DJ, DeMaria A, Kisslo J, et al. Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. Circulation 58:1072, 1978
43. Henry WL, DeMaria A, Gramiak R, et al. Report of the American Society of Echocardiography Committee on nomenclature and standards in two-dimensional echocardiography. Circulation 62:212, 1980
44. Lombard CW. Normal values of the canine M-mode echocardiogram. Am J Vet Res 45:2015, 1984
45. Boon J, Wingfield WE, Miller CW. Echocardiographic indices in the normal dog. Vet Radiol 24:214, 1983
46. Dennis MO, Nealeigh RC, Pyle RL, et al. Echocardiographic assessment of normal and abnormal valvular function in beagle dogs. Am J Vet Res 39:1591, 1978
47. Baylen BG, Garrer DJ, Laks MM, et al. Improved echocardiographic evaluation of the closed-chest canine: Methods and anatomic observations. J Clin Ultrasound 8:335, 1980
48. Franklin TD Jr, Weyman AE, Egenes KM. Closed chest canine model for cross-sectional echocardiography study. Am J Physiol 233:H417, 1977
49. Mashiro I, Nelson RR, Cohn JN, et al. Ventricular dimensions measured noninvasively by echocardiography in the awake dog. J Appl Physiol 41:953, 1976
50. Eaton LW, Maughan WL, Shovkas AA, et al. Accurate volume determination in the isolated ejecting canine left ventricle by two dimensional echocardiography. Circulation 60:320, 1979
51. Pipers FS, Andrysco RM, Hamlin RL. A totally noninvasive method for obtaining systolic time intervals in the dog. Am J Vet Res 39:1822, 1978

52. Morrison SA, Moïse NS, Scarlett JM, et al. Effect of breed and body weight on echocardiographic values of four breeds of dogs of differing weight and somatotype. J Vet Intern Med 6:220, 1992
53. Gooding JP, Robinson WF, Mews GC. Echocardiographic assessment of left ventricular dimensions in clinically normal English cocker spaniels. Am J Vet Res 47:296, 1986
54. Page A, Edmunds G, Atwell RB. Echocardiographic values in the greyhound. Austr Vet J 70:361, 1993
55. Vollmar A. Kardiologische Untersuchungen beim Irischen Wolfshund unter besonderer Berücksichtigung des Vorhofflimmerns und der Echokardiographie. Kleintierpraxis 41:397, 1996
55a. Vollmar A. Kardiologische Untersuchungen beim Deerhound, Referenzwerte für die Echodiagnostik. Kleintierpraxis 43:497, 1998
56. Sisson D, Schaeffer D. Changes in linear dimensions of the heart, relative to body weight, as measured by M-mode echocardiography in growing dogs. Am J Vet Res 52:1591, 1991
57. Bayon A, Fernández del Palacio MJ, Montes AM, et al. M-mode echocardiography study in growing Spanish mastiffs. J Small Anim Pract 35:473, 1994
58. Moïse NS, Dietze AE, Mezza LE, et al. Echocardiography, electrocardiography, and radiography of cats with dilatation cardiomyopathy, hypertrophic cardiomyopathy, and hyperthyroidism. Am J Vet Res 47:1476, 1986
59. Pipers FS, Reef V, Hamlin RL. Echocardiography in the domestic cat. Am J Vet Res 40:882, 1979
60. Jacobs G, Knight DV. M-mode echocardiographic measurements in nonanesthetized healthy cats: Effects of body weight, heart rate, and other variables. Am J Vet Res 46:1704, 1985
61. Fox PR, Bond BR, Peterson ME. Echocardiographic reference values in healthy cats sedated with ketamine hydrochloride. Am J Vet Res 46:1479, 1985
62. Soderberg SF, Boon JA, Wingfield WE, et al. M-mode echocardiography as a diagnostic aid for feline cardiomyopathy. Vet Radiol 24:55, 1983
63. Allen DG. Echocardiographic study of the anesthetized cat. Can J Comp Med 46:115, 1982
64. Sisson DD, Knight DH, Helinski C, Fox PR, et al. Plasma concentrations and M-mode echocardiographic measures in healthy cats and in cats with dilated cardiomyopathy. J Vet Intern Med 5:232, 1991
65. Jacobs G, Knight DH. Changes in M-mode echocardiographic values in cats given ketamine. Am J Vet Res 46:712, 1985
66. Fox PR, Liu SK, Maron B. Echocardiographic assessment of spontaneously occurring feline hypertrophic cardiomyopathy; An animal model of human disease. Circulation 92:2645, 1995
67. Kittleson MD, Eyster GE, Knowlen GG, et al. Myocardial function in small dogs with chronic mitral regurgitation and severe congestive heart failure. J Am Vet Med Assoc 184:455, 1984
68. Borow KM, Green LH, Mann T, et al. End-systolic volume as a predictor of postoperative left ventricular performance in volume overload from valvular regurgitation. Am J Med 68:655, 1980
69. Vuille C, Weyman AE. Left ventricle I: General considerations, assessment of chamber size and function. *In* Weyman AD (ed): Principles and Practice of Echocardiography. Philadelphia, Lea & Febiger, 1994, pp 282, 584
70. Quinones MA, Makotoff DM, Nouri S, et al. Noninvasive quantification of left ventricular wall stress. Validation of method and application to assessment of chronic pressure overload. Am J Cardiol 45:782, 1980
71. Atkins CA, Snyder PS. Systolic time intervals and their derivatives for evaluation of cardiac function. J Vet Intern Med 6:55, 1992
72. Sahn DJ. Determination of cardiac output by echocardiographic Doppler methods: Relative accuracy of various sites for measurement. J Am Coll Cardiol 6:663, 1985
72a. Choong CY. Left ventricle V: Diastolic function—its principles and evaluation. *In* Weyman AE (ed): Principles and Practice of Echocardiography. Philadelphia, Lea & Febiger, 1994, p 721
73. Carlisle CH, Wu J-X, Heath TJ. Anatomy of the portal and hepatic veins of the dog: A basis for systematic evaluation of the liver by ultrasonography. Vet Radiol Ultrasound 36:227, 1995
74. Brown DJ, Knight DH, King RR. Use of pulsed-wave Doppler echocardiography to determine aortic and pulmonary velocity and flow variables in clinically normal dogs. Am J Vet Res 52:540, 1991
75. Talano JV (ed). Doppler echocardiography in assessing intracardiac pressures, function and flow. Echocardiography 3:83, 1986
76. Richards KL. Doppler echocardiographic quantitation of stenotic valvular lesions. Echocardiography 4:289, 1987
77. DeMaria AN. Considerations in the quantification of Doppler color flow imaging. Echocardiography 4:495, 1987
78. Ritter SB. Color Doppler echocardiography–1990. Echocardiography 7:689, 1990
79. Gaber CE. Normal pulsed Doppler flow velocities in adult dogs; Abstract. Proc 5th Annu Vet Med Forum 1987, p 923
80. Yuill CD, O'Grady MR. Doppler-derived velocity of blood flow across the cardiac valves in the normal dog. Can J Vet Res 55:185, 1991
81. Kirkberger RM, Bland–van den Berg P, Grimbeek RJ. Doppler echocardiography in the normal dog: II. Factors influencing blood flow velocities and a comparison between left and right heart blood flow. Vet Radiol Ultrasound 33:380, 1992
82. Grayburn PA, Peshock RM. Noninvasive quantification of valvular regurgitation. Getting to the core of the matter. Circulation 94:119, 1996
83. Recusani F, Bargiggia GS, Yoganathan AP, et al. A new method for quantification of regurgitant flow rate using color Doppler flow imaging of the flow convergence region proximal to a discrete orifice: An in vitro study. Circulation 83:594, 1991
84. Smallhorn JF. Patent ductus arteriosus—evaluation by echocardiography. Echocardiography 4:101, 1987
85. Stevenson JB. The use of Doppler echocardiography for detection and estimation of severity of patent ductus arteriosus, ventricular septal defect, and atrial septal defect. Echocardiography 4:321, 1987
86. Switzer DF, Nanda NC. Doppler echocardiography. Part III. Congenital heart disease. Echocardiography 2:257, 1985
87. Ludomirsky A, Huhta JC (eds). Left-to-right shunts. *In* Color Doppler of Congenital Heart Disease in the Child and Adult. Mount Kisco, NY, Futura Publishing Company, NY, 1987, p 51
88. Marx GR, Allen HD, Goldberg SJ, et al. Transatrial septal velocity measurement by Doppler echocardiography in atrial septal defect. Correlation with Qp:Qs ratio. Am J Cardiol 55:1162, 1985
89. Suzuki Y, Kambora H, Kadora K, et al. Detection of intracardiac shunt flow in atrial septal defect using a real-time two-dimensional color-coded Doppler flow

imaging system and comparison with contrast two-dimensional echocardiography. Am J Cardiol 56:347, 1985
90. Curtius JM, Thyssen M, Breuer HW, et al. Doppler versus contrast echocardiography for diagnosis of tricuspid regurgitation. Am J Cardiol 56:333, 1985
91. Mikomi T, Kudo T, Sakurai N, et al. Mechanisms for development of functional tricuspid regurgitation determined by pulsed Doppler and two-dimensional echocardiography. Am J Cardiol 53:160, 1984
92. Pearlman LAS, Otto CM. Quantification of valvular regurgitation. Echocardiography 4:271, 1987
93. Pennesetti F, Loperfido F, Salvatori MP, et al. Assessment of tricuspid regurgitation by pulsed Doppler ultrasonography of the hepatic veins. Am J Cardiol 54:363, 1984
94. Wingfield WE, Boon JA, Miller CW. Echocardiographic assessment of congenital aortic stenosis in dogs. J Am Vet Med Assoc 183:673, 1983
95. Pyle RL, Patterson DF, Chacko S. The genetics and pathology of discrete subaortic stenosis in the Newfoundland dog. Am Heart J 92:324, 1976
96. Krafchek J, Robertson JH, Radford M, et al. A reconsideration of Doppler assessed gradients in suspected aortic stenosis. Am Heart J 110:765, 1985
97. Williams GA, Labovitz AJ, Nelson JG, et al. Value of multiple echocardiographic views in the evaluation of aortic stenosis in adults by continuous-wave Doppler. Am J Cardiol 55:445, 1985
98. Yeager M, Yock PG, Popp RL. Comparison of Doppler-derived pressure gradient to that determined at cardiac catheterization in adults with aortic valve stenosis: Implications for management. Am J Cardiol 57:644, 1986
99. Stamm RB, Martin RP. Quantification of pressure gradients across stenotic waves by Doppler ultrasound. J Am Coll Cardiol 2:707, 1983
100. Zoghbi WA. Echocardiographic and Doppler ultrasonic evaluation of valvular aortic stenosis. Echocardiography 5:22, 1988
101. Murphy DJ, Ludominsky A, Danford DA, Huhta JC. Doppler echocardiography in pulmonic stenosis. Echocardiography 4:187, 1987
102. Vuille C, Weyman AE. Left ventricle I: General considerations, assessment of chamber size and function. *In* Weyman AE (ed): Principles and Practice of Echocardiography. Philadelphia, Lea & Febiger, Philadelphia, 1994, p 575
103. Lombard CW. Echocardiographic and clinical signs of canine dilated cardiomyopathy. J Small Anim Pract 24:59, 1984
104. Peterson EN, Moïse NS, Brown CA, et al. Heterogeneity of hypertrophy in feline hypertrophic disease. J Vet Intern Med 7:183, 1993
105. Wingfield WE, Boon J, Miller CW. Echocardiogenic assessment of mitral valve motion, cardiac structures, and ventricular function in dogs with atrial fibrillation. J Am Vet Med Assoc 181:46, 1982
106. Louie EK. Congestive cardiomyopathy: Doppler echocardiographic assessment of structure and function. Echocardiography 4:119, 1987
107. Moise NS, Dietze AE. Echocardiographic, electrocardiographic, and radiographic detection of cardiomegaly in hyperthyroid cats. Am J Vet Res 47:1487, 1986
108. Bond BR, Fox PR, Peterson ME, Skavaril RV. Echocardiographic findings in 103 cats with hyperthyroidism. J Am Vet Med Assoc 192:1546, 1988
109. Bonagura JB, Fox PR. Feline restrictive cardiomyopathy. *In* Bonagura JB, Kirk RW (eds): Kirk's Current Veterinary Therapy. Vol 12. Philadelphia, WB Saunders, 1995, p 863
110. Fox PR. Feline myocardial diseases. Proc 18th Annu Waltham/OSU Symp. Cardiology. Vernon, CA, Waltham USA, Inc. 1994, p 117
111. Liu SK, Fox PR, Bond BR. Restrictive cardiomyopathy in the cat; Abstract. 8th Asian-Pacific Cong Cardiol, 1983
112. Bonagura JD, Pipers FS. Echocardiographic features of aortic valve endocarditis in a dog, a cow, and a horse. J Am Vet Med Assoc 182:595, 1983
113. Lombard CW, Buergelt CD. Vegetative bacterial endocarditis in dogs: Echocardiographic diagnosis and clinical signs. J Small Anim Pract 24:325, 1983
114. Bonagura JD, Pipers FS. Echocardiographic features of pericardial effusion in dogs. J Am Vet Med Assoc 179:49, 1981
115. Bonagura JD. Electrical alternans associated with pericardial effusion in the dog. J Am Vet Med Assoc 178:574, 1981
116. Sagar KB, Wann LS, Klopefenstein HS. Echocardiography in the diagnosis of cardiac tamponade. Echocardiography 4:29, 1987
117. Thomas WP, Sisson D, Bauer TG, et al. Detection of cardiac masses in dogs by two-dimensional echocardiography. Vet Radiol 25:65, 1984
118. Lombard CW, Buergelt CD. Echocardiographic and clinical findings in dogs with heartworm-induced cor pulmonale. Comp Cont Educ 5:971, 1983

9

Cardiac Catheterization and Angiocardiography

WILLIAM P. THOMAS
DAVID SISSON

HISTORICAL PERSPECTIVES

The "gold standard" for cardiovascular diagnosis over the past several decades has been invasive hemodynamic measurement and visualization of cardiac and vascular blood flow via catheters introduced through peripheral blood vessels (i.e., cardiac catheterization).[1] Many disorders that once required catheterization for confirmation can now be diagnosed noninvasively by multimodal echocardiography. In fact, reliable diagnosis, prognosis, and therapy can now be accomplished in most patients by noninvasive evaluations, which include physical examination, thoracic radiography, electrocardiography, and echocardiography (especially if it includes Doppler imaging). However, cardiac catheterization remains an important clinical and research tool best performed and interpreted by individuals with specialty training or experience in cardiology and radiology.

Although dogs have been used extensively for cardiovascular research, few references discuss the details of clinical cardiac catheterization.[2–6] The techniques and applications in animals are similar to those used in humans; in-depth coverage of this topic can be found in several human texts.[7–11]

INDICATIONS

The decision to perform cardiac catheterization should be based on careful consideration of potential risks versus benefits. Most catheterization and angiographic procedures require general anesthesia, which may have attendant risks, although in experienced hands, morbidity and mortality with catheterization is modest if overt heart failure is not present. The cost of the study, which requires specialized equipment and expertise, must also be considered.

Invasive studies should be used in those instances in which an understanding of the anatomic and physiologic abnormalities from noninvasive studies are inadequate or incomplete for making clinical decisions. Such instances may include (1) animals in which measurement of intracardiac pressures, especially diastolic pressures, may affect the diagnosis, recommended therapy, or prognosis; (2) animals with vascular disorders affecting the great vessels or systemic, pulmonary, or coronary vasculature, which cannot be adequately evaluated noninvasively; and (3) animals with congenital or ac-

quired heart disease that requires additional characterization in preparation for cardiac surgery. In addition, catheterization is required to perform interventional procedures, such as balloon dilation of intracardiac or vascular obstructions, transcatheter vascular interventions, and electrodiagnostic studies. Direct measurement of cardiac output and intracardiac pressures by catheterization are also commonly performed as part of clinical and experimental research protocols.

CONTRAINDICATIONS

There are no absolute contraindications to cardiac catheterization except for severe adverse reactions to anesthesia. In general, if the risk of the procedure outweighs the potential benefit of the data obtained, the study is not indicated. Catheterization is not indicated when an adequate diagnosis has been made noninvasively, except as a research or instructional procedure with the owner's informed consent. Potentially severe arrhythmias or congestive heart failure should be under maximum medical control prior to the study. In addition, any correctable extracardiac conditions that might affect the study results or increase the risk of the procedure, especially pulmonary diseases, bleeding disorders, hyperthyroidism, anemia, and fluid–electrolyte–acid base abnormalities, should be treated prior to the study.

CARDIAC CATHETERIZATION—METHODOLOGIES AND TECHNIQUES

EQUIPMENT

Cardiac catheterization is a sophisticated procedure requiring special monitoring and recording equipment. Placement of catheters and angiography are carried out under fluoroscopic guidance with image intensification to minimize radiation exposure. The image is displayed on a television monitoring system. Either the table top or the x-ray unit should be adjustable to optimize animal positioning.

Display and recording of physiologic data are accomplished using a multichannel amplifier-recorder that allows continuous electrocardiographic (ECG) monitoring and recording of two or more parameters simultaneously. Anesthesia equipment is required. A direct-current defibrillator, emergency drugs, and cardiopulmonary (CPR) equipment should be readily available.[10] A variety of catheters, surgical instruments, drapes, and suture material should be presterilized. Other studies such as indicator dilution and oximetry require equipment described later.

During catheterization, electrical grounding and shielding from x-radiation are essential for patient and operator safety. Cardiac catheters provide direct pathways to the heart, and current leaks from x-ray or recording equipment have the potential to cause arrhythmias or even ventricular fibrillation.

PATIENT PREPARATION AND ANESTHESIA

Although limited catheterization may be accomplished in awake or lightly sedated patients, full catheterization is usually performed under general anesthesia (chapter 38). Routine laboratory evaluation, including a complete blood count and BUN or creatinine is obtained prior to anesthesia. Cardiac medications are often withheld on the morning of the study. Most sedatives and anesthetics reduce cardiac output and blood pressure to some degree, and an attempt should be made to minimize these effects. Premedication with atropine or glycopyrrolate[12] may be given along with a small dose of a narcotic or other sedative. Tranquilizers tend to depress blood pressure more than narcotics. Barbiturates have less effect on cardiac output and blood pressure, but their use involves the risks associated with longer-acting, less reversible intravenous drugs. Endotracheal intubation is advocated, and equipment for positive-pressure ventilation and oxygen administration should be available. The most common methods use inhalation anesthesia with methoxyflurane, halothane, or isoflurane.[13, 14] Close ECG monitoring is important. The level of anesthesia should be as light as possible to minimize the drugs' hemodynamic effects, and light anesthesia just sufficient to prevent movement is usually adequate.

Cardiac catheterization is a minor surgical procedure requiring aseptic technique. All catheters, surgical instruments, drapes, and other equipment that will contact the operator or patient should be presterilized, and the surgical site is clipped, surgically prepped, and draped.

There are several methods to introduce catheters and reach the desired chambers and vessels.[2–10] Older, cruder techniques, such as direct transthoracic left ventricular needle puncture, are rarely used today. Almost all cardiac catheterizations are performed using percutaneous techniques or surgical exposure of peripheral vessels ("cut-down") to introduce catheters directly, which are then guided through the circulation using fluoroscopic guidance.[7–10]

PERCUTANEOUS CATHETERIZATION

Percutaneous catheter insertion (sometimes referred to as the Seldinger technique[8]) without a cut-

down is used extensively in humans, but it is employed in animals primarily for right-sided heart catheterization. The technique begins with percutaneous needle puncture of a peripheral vein or artery and introduction of a flexible guidewire through the needle into the vessel. The needle is removed, leaving the wire in place. In the original technique, after a short, tapered dilator is fed over the wire to enlarge the path and then removed, a tapered end-hold catheter is guided over the wire into the vessel and the catheterization proceeds. Today it is much more common to introduce a commercial dilator-sheath combination over the guidewire to dilate the path and to position a self-sealing sheath in the vessel, through which catheters may be easily introduced and exchanged. When the catheters and sheath are removed at the end of the procedure, patient immobility and direct vascular pressure are required to prevent excess hemorrhage, especially after arterial puncture. Since this is usually not possible to achieve easily in small animals, percutaneous catheterization is usually limited to peripheral venous entry for right-sided heart catheterization, whereas peripheral arterial entry for left-sided heart catheterization is more often achieved by direct arterial cut-down.

VASCULAR CUT-DOWN

Passage of vascular catheters in the No. 4 to 10 French range requires access to large arteries and veins. The most commonly selected vessels because of their size, mobility, and proximity to the heart are the carotid artery and external jugular vein in the neck.[5, 6] The proximal femoral artery and vein are also used, but they lie farther from the heart and are less mobile than those in the neck. The femoral approach may be preferred for transseptal left heart catheterization, for electrode catheters for some electrophysiologic studies, and for some interventional studies.

The technique of catheter insertion is the same at either site. Accordingly, a small 2- to 3-cm incision is made through the skin and subcutaneous tissue. In the neck, the external jugular vein, which lies in the superficial fat ventrolateral to the trachea, and the carotid artery, which lies deeper and dorsolateral to the trachea, are isolated by blunt dissection. The artery is separated from the small internal jugular vein and large vagosympathetic trunk. In the hind limb, the femoral artery, vein, and nerve lie together just cranial to the pectineus muscle. The nerve is carefully separated, and the artery and vein are separately isolated.

To insert the catheter, the vessel is either ligated distally or occluded by means of a rubber or elastic band held with a hemostat. A similar band is applied proximally, and the vessel is tensed slightly between the bands. A small incision is made in the vessel through which the catheter is inserted. The proximal band is loosened to allow passage of the catheter and then clamped around the catheter and vessel to prevent bleeding but loose enough to allow easy manipulation of the catheter. When a catheter is in a blood vessel, it is flushed periodically with heparinized (1 to 2 IU/ml) saline.

CATHETERS AND GUIDEWIRES

Many different catheter configurations have been designed for specific purposes. The catheter selected depends on the studies that are planned and the operator's experience and personal preference. A variety of catheter lengths, diameters, and tip configurations (Fig. 9–1) should be available. The ideal catheter is radiopaque for easy fluoroscopic visualization, relatively nonthrombogenic, smooth enough to slide easily through the vessel, flexible enough to bend without kinking and reduce the risk of perforation, yet stiff enough so that the tip can be easily controlled by manipulating the proximal catheter end. The most common materials used are woven Dacron and polyethylene.[7–10]

Catheters used in small animals usually range from No. 4 French (1.3 mm) to No. 8 French (2.7 mm) outside diameter and 50 to 150 cm in length.[2–6] In general, the largest-bore catheter that can be easily introduced through the peripheral vessel and maneuvered to all desired positions is the best to use, allowing easy injection and withdrawal with the least resistance.

CATHETER SELECTION

When a catheter is selected, a few general rules should be applied. Pressure may be measured with plain catheters having either an end hole, one or more side holes, or both (Fig. 9–1*A*). To measure pulmonary capillary wedge pressure, a plain end-hold catheter (e.g., Cournand's catheter) or a balloon-tipped end-hole catheter (Swan-Ganz type) (Fig. 9–1*A*,*B*) is usually used. An end hole is also required for any catheter inserted over a guidewire. A multipurpose, balloon-tipped, end- and side-hole thermistor catheter (Fig. 9–1*B*) is also commonly used to measure pulmonary artery and right atrial pressures and thermodilution cardiac output in the laboratory or in an intensive care unit. For rapid angiographic contrast injection, especially when using an automated power injector, a catheter with side holes and a closed or tightly curved tip (e.g., NIH, Lehman's ventriculography, Berman's angiographic, or pigtail) is recommended. Multiple, symmetrically opposed lateral holes and lack of an

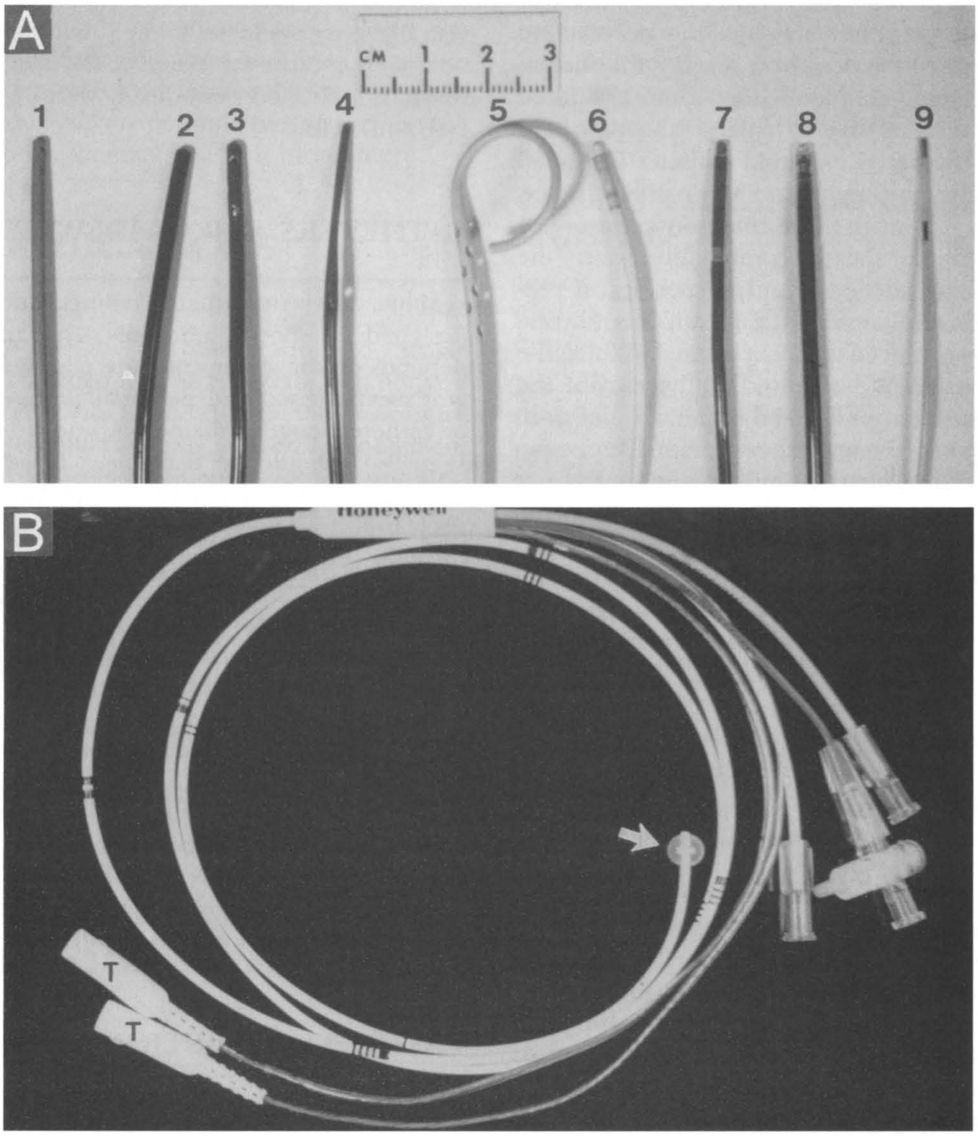


FIGURE 9–1

(A) The tips of some commonly used cardiovascular catheters are illustrated. 1, Straight polyethylene tubing with an end hole and a manually cut side hole; 2, Cournand's dacron catheter with an end hole only; 3, NIH angiographic catheter with several side holes just proximal to a blunt, closed tip; 4, Lehman's ventriculography catheter with a tapered solid but flexible tip and 2 side holes just proximal to the taper; 5, pigtail catheter with multiple side holes proximal to a tightly curved tip with an end hole; 6, Swan-Ganz type of balloon-tipped catheter with inflatable balloon cuff at the tip and an end hole (used primarily for right-sided heart catheterization and pulmonary arterial wedge pressure measurement); 7, bipolar electrode catheter for recording His bundle electrograms; 8, Telco catheter with micromanometer tip for high-fidelity recording of pressure and intracardiac phonocardiography; 9, thin, bipolar electrode catheter for temporary cardiac pacing. (B) Balloon-tipped thermodilution catheter. The three ports on the right communicate with the end hole, a side hole several centimeters from the tip, and the balloon at the tip *(arrow)*, respectively. The other 2 plug connectors *(T)* are the electrical connections to a thermistor near the catheter tip used for cardiac output measurement by thermal indicator dilution.

end hole allow better dispersion of injected contrast material, stabilize the catheter tip, and allow injection without the catheter recoil that invariably accompanies rapid injection through an end-hold catheter. In addition, there is reduced risk of intramyocardial injection of contrast if the catheter tip is positioned against the myocardium.

GUIDEWIRE SELECTION

Guidewires are inserted into vascular catheters to assist their manipulation and insertion. They are similar to wound guitar strings, consisting of a solid steel wire core wrapped in a fine wire coil. The most commonly used guidewires range in length from 125 to 260 cm, and in diameter from 0.01 to 0.38 mm. The tip, which lacks the solid inner core and is very flexible, may be straight or curved into a sharp J shape to further reduce the risk of perforation.

Flexible guidewires are useful for (1) maneuvering a catheter into a desired position more easily than if a stiffer catheter were selected; (2) straightening a curved catheter to facilitate its insertion or maneuvering; (3) maintaining percutaneous vessel access during catheter exchange; and (4) preplacement to guide large-bore, stiff catheters. They are particularly useful and even essential for guiding balloon dilation catheters, which are typically stiff and wide, especially in the region of the balloon. Also available are steerable guidewires that have a proximal control mechanism that allows the operator to control the flexion of the tip. These may be advantageous in very small patients in which maneuvering room in the heart is very limited.

RIGHT-SIDED HEART CATHETERIZATION

Right-sided heart catheterization is accomplished through an external jugular or femoral vein. Whether the right or left side is used and whether the animal faces left or right is a matter of personal preference. Because of the low venous blood pressure, little physical pressure is required from the occluding bands placed on the vessel to prevent hemorrhage. After achieving vascular access and catheter introduction, the animal's thorax is positioned in the fluoroscopic beam field for further guidance.

From the jugular venous approach (Fig. 9–2*A*–*D*), the catheter is advanced down the jugular vein, through the cranial vena cava, and into the right atrium (Fig. 9–2*A*). In the atrium, the tip is directed ventrally into the right ventricle (Fig. 9–2*B*) and then cranially to reach the right ventricular outflow tract and pulmonary artery (Fig. 9–2*C*), forming a loop. Preforming the catheter with curvature at the tip facilitates this maneuver. Misdirection of the catheter in the vena cava or atrium may result in its passage dorsally into the azygos vein or caudally into the caudal vena cava or coronary sinus. The pulmonary capillary or arterial "wedge" position is attained by advancing the catheter distally into the lung until its tip is wedged into a small pulmonary artery, occluding forward flow through the vessel (Fig. 9–2*D*). Alternatively, a balloon-tipped catheter can be positioned in a medium pulmonary arterial branch and the balloon inflated to occlude forward flow and record the back pressure from the pulmonary capillaries and veins (the "*wedge*" pressure). A similar course is followed if the femoral approach is used.

Right-sided heart catheterization may also be achieved without fluoroscopic visualization, primarily in large dogs, by using a balloon-tipped catheter (Fig. 9–1*B*). When the balloon is inflated in the right atrium, the catheter tip tends to be swept with the blood flow into the right ventricle and pulmonary artery. Positioning in the atrium, ventricle, pulmonary artery, or wedge position can be confirmed by connecting the catheter to a pressure transducer (Fig. 9–3) and monitoring the configuration of the pressure pulse, or by a small test injection of contrast medium. Normal right-sided heart pressures are shown in Figure 9–4 and Table 9–1.

LEFT-SIDED HEART CATHETERIZATION

PERIPHERAL ARTERIAL APPROACH

Left-sided heart catheterization is accomplished through a carotid or femoral artery. Because of the high arterial blood pressure, extra care must be taken to ensure that the occluding bands placed on these

TABLE 9–1
Normal Intracardiac and Intravascular Pressures (mmHg) in Small Animals

Site	Systolic	Diastolic	Mean
RA	—	—	3 (±2)
RV	25 (±5)	0–5	—
PA	25 (±5)	10 (±3)	15 (±5)
PA wedge	6 (±2)	4 (±2)	5 (±2)
LA	—	—	—
LV	120 (±20)	0–8	—
Aorta	120 (±20)	90 (±10)	100 (±10)
Femoral artery	130 (±20)	90 (±10)	100 (±10)

Note: These values represent animals under intravenous pentobarbital anesthesia. Somewhat lower values are common in animals given other preanesthetic and anesthetic agents.

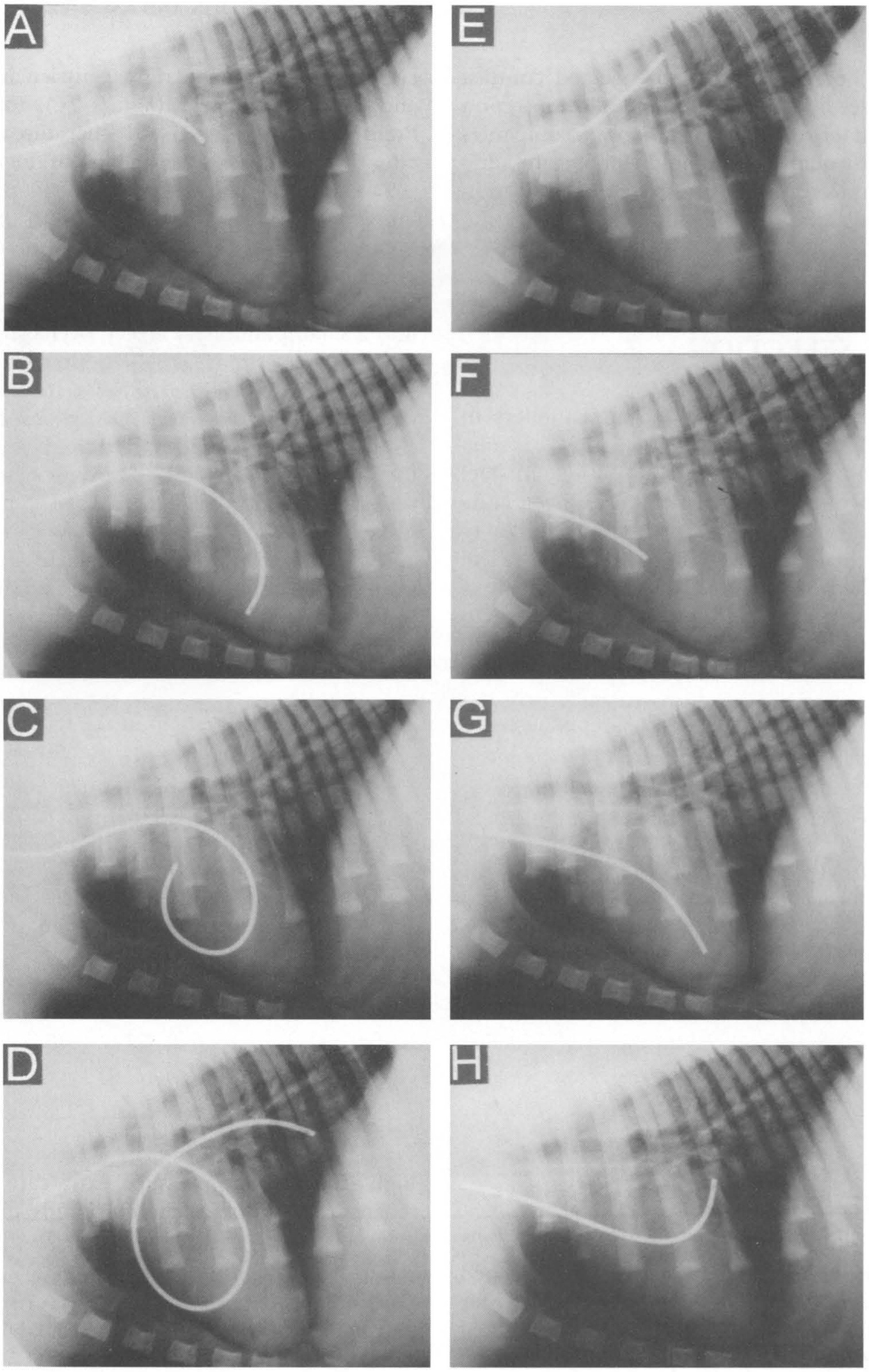


FIGURE 9–2

(A–D) *Right-sided heart catheterization via the external jugular vein* is illustrated. Using fluoroscopic guidance, the catheter is advanced through the cranial vena cava into the right atrium (A), then ventrally through the tricuspid valve into the right ventricle (B). From the RV the catheter must turn cranially into the RV outflow tract, then dorsally through the pulmonary valve into the proximal pulmonary artery (C). The pulmonary wedge position is reached by advancing the catheter farther into a smaller pulmonary artery (D). (E–H) *Left heart catheterization via the carotid artery* is illustrated. The catheter tip is guided retrograde through the brachiocephalic trunk into the aortic arch, then dorsally into the descending aorta (E) or ventrally into the ascending aorta (F) and through the aortic valve into the left ventricle (G). Although difficult to achieve in very small patients, the catheter tip may be guided dorsally through the mitral valve into the left atrium (H). Compare these positions with the angiograms in Figures 9–11 and 9–12.

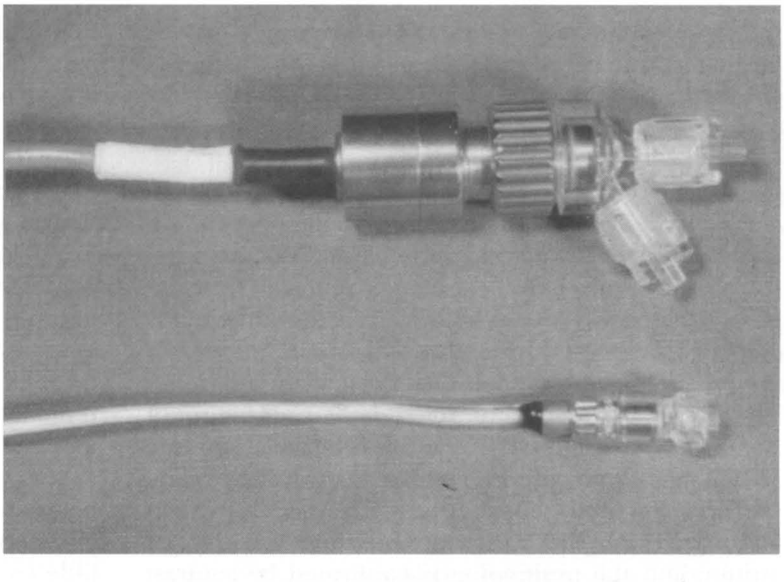


FIGURE 9–3

Examples of Statham pressure transducers. The larger model, p23Db, is useful for small and large animals, whereas the smaller model, p37B, is more fragile and used mainly for very small animals. Pressure is measured by connecting the end of the fluid-filled transducer dome horizontally to the fluid-filled intravascular catheter to form a closed, gas-free fluid connection between the catheter tip and transducer sensing diaphragm.

vessels are tight and stable enough to prevent hemorrhage during catheter manipulations.

From the cervical approach (Fig. 9–2*E–H*), the catheter is advanced through the brachiocephalic trunk and into the aortic arch. By turning the tip dorsally or ventrally, the catheter can be directed into the descending (Fig. 9–2*E*) or ascending (Fig. 9–2*F*) aorta, respectively. In the aortic root, the catheter tip tends to deflect off the aortic valve cusps into the sinuses of Valsalva. Repeated back-and-forth movements timed to advance the catheter during ventricular systole usually result in passage through the valve into the left ventricle (Fig. 9–2*G*). If the catheter has an end hole, use of a J-tipped guidewire may assist in this maneuver. Several catheters have been designed to facilitate retrograde passage through the aortic valve, including Lehman's ventriculography and pigtail catheters (Fig. 9–1).[7–10] Ventricular arrhythmias are commonly induced by the catheter tip in the left ventricle, and the ECG should be continuously monitored to detect and avoid serious arrhythmias. Because of the difficulty passing a catheter retrograde through the mitral valve, the left atrium is not routinely catheterized. However, using a flexible and slightly curved catheter turned dorsally in the ventricle, the left atrium may be entered (Fig. 9–2*H*).

Left-sided heart catheterization is usually more difficult from the femoral approach because of the greater distance involved and the curvature of the aortic arch, which reduce the operator's control over

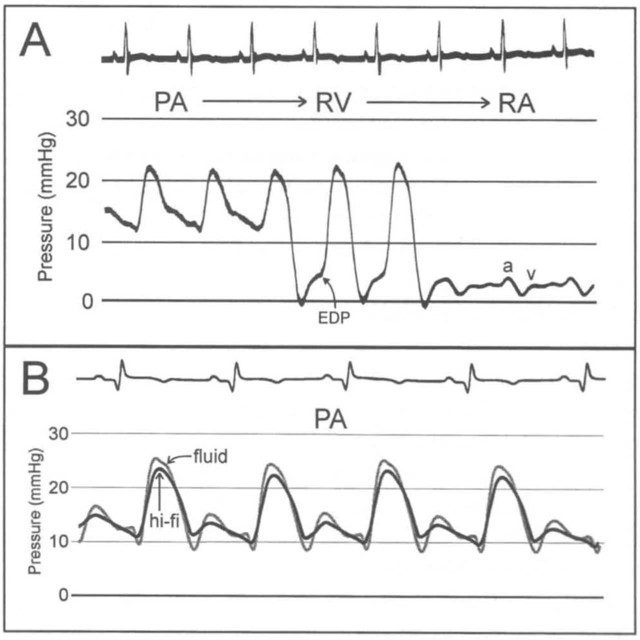


FIGURE 9–4

(A) Normal right-sided heart pressures during withdrawal of a catheter from the pulmonary artery *(PA)* into the right ventricle *(RV)* and right atrium *(RA)*. As the catheter tip crosses the pulmonary valve, the early diastolic pressure drops to near zero in the right ventricle. The peak systolic pressure in the PA and RV is the same (22 mmHg), with no pressure gradient across the normal valve. The RV end-diastolic pressure (EDP = 4 to 5 mmHg) is measured after atrial systole, just before the rapid upstroke of ventricular systole *(arrow)*. As the catheter tip crosses the tricuspid valve, the systolic pressure also drops to a low level. In the RA, the *a* wave is due to atrial contraction, and the *v* wave represents atrial filling during later ventricular systole. The mean RA pressure is 3 mmHg. (B) Pulmonary artery pressure recorded simultaneously by a fluid-filled catheter system and a high-fidelity catheter-tip manometer system. Note the smoother, high-fidelity tracing and the exaggerated peaks and fluctuation on the fluid-filled catheter tracing (see text for details).

the catheter tip. Passage into the left ventricle may be facilitated using a pigtail catheter and/or a J-tipped guidewire.

TRANSSEPTAL APPROACH

An alternative but infrequently used method to catheterize the left atrium and ventricle utilizes the atrial transseptal approach.[7–10] Using a femoral vein approach, a specially designed long needle with a gently curved tip is passed through an end-hole catheter to the junction of the caudal vena cava and right atrium. The needle is advanced to protrude beyond the tip of the catheter, aimed medially toward the atrial septum, and then fluoroscopically positioned against the fossa ovalis in the caudal right atrium. The needle is then advanced through the interatrial septum into the left atrium, and the positioning is confirmed by contrast injection or by demonstrating a high oxygen content in a blood sample. A guidewire can then be passed through the needle and used to guide other catheters into the left atrium and ventricle after needle removal. Transseptal puncture may also be accomplished using the jugular vein approach. The transseptal approach is most valuable in conditions in which the left atrium and ventricle cannot be reached by retrograde catheterization (e.g., mitral stenosis or severe aortic stenosis).

RECOVERY AND AFTERCARE

Following completion of appropriate studies, catheters are removed and the vessels are repaired or ligated, depending on the vessel size, degree of damage incurred, length of the procedure, and ability of the operator. Free bleeding should occur from both proximal and distal portions of a vessel to be repaired. Fortunately, because of the presence of collateral paths, the jugular vein, carotid artery, and femoral artery and vein may be safely ligated in dogs and cats. Wound closure and aftercare are routine. Perioperative antibiotics are not recommended unless the procedure is long or the sterility is compromised.

COMPLICATIONS

In experienced hands and with proper precautions, serious complications during or after cardiac catheterization are uncommon.[1, 15–18] Risk is definitely increased in the presence of heart failure, and risks also tend to increase in proportion to procedure length, disease severity, and aggressiveness of the procedure (e.g., balloon dilation).

Complications may be minor and transient or major and serious.[15] The most common transient complication is an atrial or ventricular arrhythmia, usually premature beats or transient ventricular tachycardia, induced by catheter contact of sensitive endocardium. An especially sensitive area for catheter-induced ventricular arrhythmias is the right ventricular outflow tract. These usually subside when the catheter is withdrawn or repositioned, but lidocaine administration may be indicated if ventricular ectopy is marked and persistent. Right bundle branch block may also be induced when a right-sided heart catheter (especially a large, balloon dilation catheter) is manipulated through the right ventricular outflow region, due to trauma to the right bundle branch within the thin moderator band. This usually subsides within minutes to a few hours, but permanent bundle branch block occasionally results. Intimal damage and thrombosis may occur in catheterized vessels, but this is usually of little consequence. Post-operative complications at the incision site may include hemorrhage, infection, or seroma formation, which rarely requires drainage.

Serious, potentially life-threatening complications, although uncommon in an experienced laboratory, may include ventricular fibrillation, cardiac or vascular perforation, valve damage, intramyocardial contrast injection, and catheter breakage and embolus.[10, 15–17] Myocardial infarction, a significant risk in humans, is extremely rare in animals. Occasionally, a catheter-induced ventricular arrhythmia may progress to ventricular fibrillation. Emergency drugs and a defibrillator should always be nearby during any invasive cardiac study. Overzealous catheter manipulation may result in perforation of the myocardium or a large vessel, resulting in thoracic hemorrhage or acute cardiac tamponade. A catheter should never be forced against an obstruction. Use of flexible, preformed catheters, judicious use of guidewires, and gentle manipulation can minimize this risk. Vigorous catheter manipulation can also perforate or lacerate a cardiac valve, especially during retrograde catheterization or balloon catheter dilation. Particular care is required when passing a catheter retrograde through the delicate aortic valve.

Complications associated with angiocardiography are uncommon in experienced laboratories.[10, 15, 18, 19] Transient hypotension is common following angiography, and the risk of severe hypotension, bradycardia, and acute heart failure is increased in patients with severe acquired pulmonary hypertension. Intramyocardial injection of contrast medium can occur, usually when a power injector is used with an end-hole catheter or with any catheter wedged into ventricular trabeculae. Use of closed tip, side-hole catheters for angiography and confirming catheter tip positioning by small test injections of contrast by hand usually prevents this complication. Catheters that are intended for reuse should also be inspected after every use for cracks, kinks, or weakened areas, especially near the tip, to prevent breakage and embolization.

CARDIAC CATHETERIZATION STUDIES

The commonest studies performed include pressure measurements, blood sampling for oximetry, indicator dilution flow studies, and angiocardiography.[3, 5–11] Less commonly, intracardiac phonocardiography, intracardiac electrogram recording and pacing studies, and interventional studies (e.g., balloon dilation valvuloplasty, transvenous coil occlusion) are performed.

PRESSURE MEASUREMENTS

Intracardiac hydrostatic pressure is the most common hemodynamic measurement made at cardiac catheterization.[5–11] As a general rule, all hemodynamic studies, including pressure measurements, should be performed prior to angiography and under very light anesthesia to minimize the negative hemodynamic effects of these agents. While micromanometer-tipped catheters provide lag-free and nearly artifact-free pressure recording (Fig. 9–4*B*), they are expensive and fragile. The most common system used in clinical studies is the fluid-filled catheter coupled to an external strain gauge transducer-amplifier-recorder system (Figs. 9–1, 9–3).

There are several principles to consider when measuring pressure with a fluid-filled catheter-transducer system.[8–11] The transducer consists of a pressure-sensitive membrane or diaphragm inside the fluid-filled chamber with one or two outlet connections (Fig. 9–3). Changing pressure at the catheter tip is transmitted by small fluid movements through the catheter directly to the transducer chamber. When this pressure change is applied to the diaphragm, changes in electrical resistance proportional to the pressure cause voltage changes in a circuit beneath the diaphragm. The transducer thereby converts the intravascular pressure signal into a proportional voltage signal that can be calibrated, displayed on an oscilloscope, and recorded on paper or tape. For the system to display the catheter tip pressure accurately, the following criteria must be met:[8–11]

1. The transducer must accurately calibrate and zero properly compared with a mercury manometer, and its response must be linear over the range of intravascular pressures. The zero level should be checked frequently during the procedure to compensate for baseline drift, usually caused by temperature changes in the transducer dome.
2. The catheter tip and transducer must be at the same vertical level (especially important for accurately measuring low atrial and ventricular diastolic pressures), usually standardized at the midsternal level in a laterally recumbent animal.
3. The frequency response of the entire system must be appropriate. For intravascular pressures, a relatively flat, linear (± 5 percent) frequency response (output vs. input) up to the frequency of the first 10 harmonics (approximately 20 Hz) of the fundamental frequency of the pressure wave is required.

Every catheter-transducer system has its own natural frequency at which the system resonates and overamplifies the signal. That frequency should be higher than 20 Hz to avoid accentuation of the higher frequency components of the pressure signal and "overshoot"-type artifacts. Damping of higher frequencies is often necessary to limit this type of artifact. However, if the system is overdamped, the higher-frequency components of the pressure signal are diminished and smaller, more rapid pressure fluctuations are lost, altering the peak systolic and diastolic portions of the tracing. Common causes of overdamping include air bubbles in the system, clots in the catheter tip, fluid leaks, a catheter that is too narrow or too long for the volume of the transducer, and other hindrances to free fluid movement (e.g., kinked catheter, partially closed stopcock). The commonly employed No. 4 to 8 French catheter–transducer systems, although inadequate for recording high-frequency events (such as ventricular dp/dt [rate of change of pressure]), are usually satisfactory for recording conventional clinical pressures.

Pressure is recorded from each chamber entered during the procedure. Before recording the first pressure, the zero reference point and system calibration are rechecked and the catheter is flushed. The catheter tip should be free in the lumen of the vessel or chamber (except in the wedge position) to prevent occlusion of the hole(s) during part of the cardiac cycle, which is especially common with end-hole catheters. The catheter tip should also be as stable as possible to avoid motion artifact ("catheter whip"), which is especially common in tracings from the pulmonary artery. On the venous (right) side, the pulmonary wedge pressure is measured as described earlier, using an end-hole or balloon-tipped catheter. By occluding forward flow, the end hole measures the back pressure from the pulmonary capillaries, veins, and left atrium. The tracing resembles left atrial pressure (*a* and *v* waves may or may not be discernible) and is slightly lower than the pulmonary artery diastolic pressure. The catheter is then withdrawn successively into the pulmonary artery, right ventricle, and atrium. It is common to encounter ventricular extrasystoles when the catheter tip crosses the pulmonary valve into the right ventricular outflow tract. On the arterial (left) side, pressure is recorded during withdrawal of the catheter tip from the left ventricle into the aorta. A

catheter with a single end or side hole is most useful if both the magnitude and location of an abrupt pressure change (*pressure gradient*) are being studied.

CARDIOVASCULAR PRESSURE VALUES

Normal cardiac pressures are listed and illustrated (Table 9–1; Figs. 9–4, 9–5).[11] Arterial pressure tracings in the normal animal have a peak systolic pressure, a dicrotic notch associated with semilunar valve closure, and a minimum diastolic pressure. The pulmonary artery diastolic pressure should be very close to the left ventricular end-diastolic pressure. In the ventricle, the systolic pressure is the same as in the corresponding artery, but the diastolic pressure is similar to atrial pressure and close to zero. The end-diastolic ventricular pressure is measured after atrial contraction at the junction between the *a* (atrial contraction) wave and the rapid, early systolic upstroke. The atrial pressure tracing is only a few millimeters of mercury and has two consistent positive waves, *a* and *v* (late systole), followed by the downslopes *x* and *y*, respectively.

Relatively few major changes in the normal pressure profiles are commonly recorded in patients with heart disease.[2–11] Examples of abnormal pressure tracings from animals with right-sided and left-sided heart diseases are illustrated (Figs. 9–6, 9–7; see also Figs. 24–1, 24–11, 24–20, 24–21; Figs. 29–1, 29–13, 29–14, 29–21, 29–22). Abnormalities of systolic pressure occur primarily when there is an increased resistance to ventricular outflow. Discrete flow obstructions anywhere in the circulation are characterized by the presence of a pressure gradient during flow across the obstruction. Discrete ventricular outflow obstructions are diagnosed by demonstrating a systolic pressure gradient across the obstruction, which may be valvular, subvalvular, or supravalvular, and may be fixed or dynamic.[1, 7–11]

Figures 9–6*A* and 9–7*A* demonstrate typical systolic gradients from dogs with valvular pulmonic stenosis[18] and subvalvular aortic stenosis,[19] respectively. Atrioventricular valve obstructions (rare) are similarly characterized by a pressure gradient between the atrium and ventricle during diastole.[20] Diseases that diffusely in-

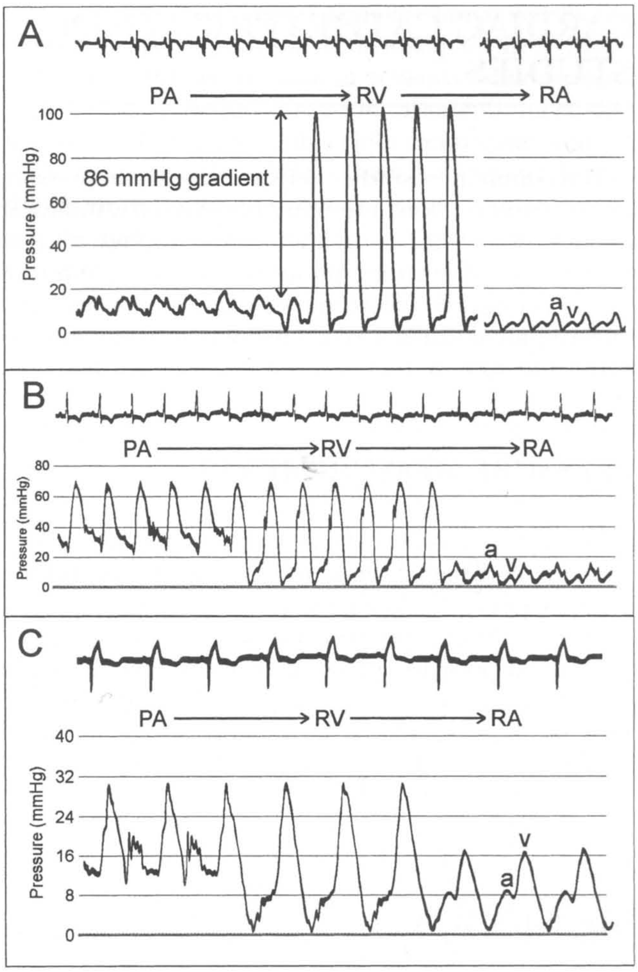


FIGURE 9–6

Abnormal right-sided heart pressure tracings. (A) Dog with congenital pulmonic stenosis. The pulmonary artery pressure is normal, but there is an abrupt increase in the systolic pressure as the catheter tip is withdrawn across the valve into the right ventricle (compare with Fig. 9–4*A*). The systolic pressure gradient is 86 mmHg, indicating a moderately severe stenosis at the pulmonary valve level. The mean right atrial pressure is normal (4 to 5 mmHg), but the *a* wave is slightly increased because of the associated right ventricle *(RV)* hypertrophy. (B) Dog with moderate pulmonary hypertension. The systolic, diastolic, and mean pulmonary artery *(PA)* pressures are increased. The systolic pressure is also increased in the RV, and there is no gradient across the pulmonary valve. The RV end-diastolic pressure is increased (12 to 15 mmHg), and the right atrial *a* wave is also prominent. (C) Dog with tricuspid valve regurgitation. The PA pressure and the RV systolic pressure are normal. The RV end-diastolic pressure is slightly increased (8 to 9 mmHg). The mean right atrium *(RA)* pressure is slightly increased (7 mmHg), and the *v* wave is increased (17 mmHg) and dominant.

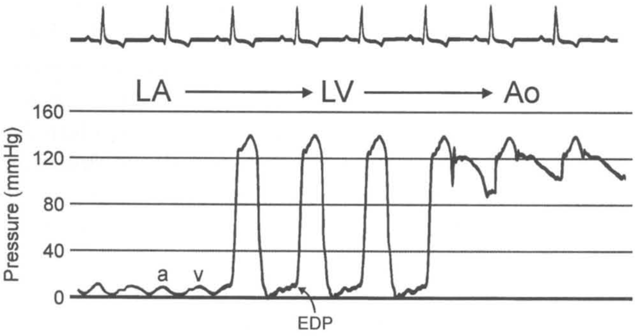


FIGURE 9–5

Normal left-sided heart pressures during withdrawal of a catheter from the left atrium *(LA)* through the left ventricle *(LV)* into the aorta *(Ao)*. The LA tracing is similar to that in the RA (Fig. 9–4). In the LV, the end-diastolic pressure (EDP = 8 mmHg) is slightly higher than in the RV (Fig. 9–4). As the catheter tip crosses the aortic valve, the diastolic pressure increases (105 mmHg). The peak systolic pressure in the Ao and LV is the same (140 mmHg), with no pressure gradient across the normal valve. The sharp deflection at the dicrotic notch of the first aortic pressure pulse is an artifact caused by the aortic valve impacting on the catheter tip.

crease peripheral systemic vascular resistance or pulmonary vascular resistance result in increases in the corresponding mean arterial pressure (systemic hypertension or pulmonary hypertension,[21] respectively) and identical increases in the corresponding arterial and ventricular systolic pressure (Fig. 9–6*B*; note that there is no systolic pressure gradient across the semilunar valve in this case).

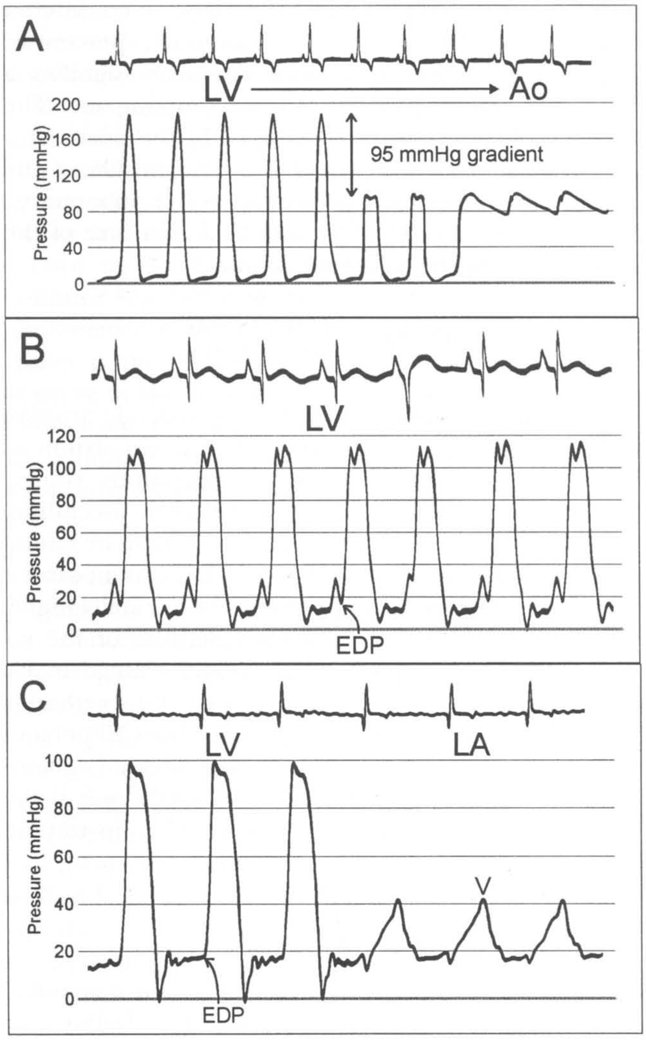


FIGURE 9–7

Abnormal left-sided heart pressure tracings. (A) Dog with congenital subaortic stenosis. The systolic pressure in the body of the left ventricle *(LV)* is increased (185 mmHg). As the catheter tip is withdrawn from the LV, there is an abrupt decrease in systolic pressure while the catheter is still in the LV (pressure gradient = 95 mmHg), indicating a subvalvular obstruction. Further catheter withdrawal across the aortic valve shows no systolic gradient at the valve level. (B) Dog with dilated cardiomyopathy and congestive heart failure. The LV end-diastolic pressure *(EDP)* is elevated (19 to 20 mmHg), whereas systolic pressure remains normal. The notch at the peak of LV pressure is a common fluid-filled catheter artifact. (C) Dog with congenital mitral valve dysplasia, atrial fibrillation, and severe mitral regurgitation. The LV systolic pressure is normal. The LV end-diastolic pressure is elevated (18 to 19 mmHg). The mean left atrium *(LA)* pressure is increased (25 mmHg), and the *v* wave is markedly increased (41 mmHg) and dominant. Note that there is no *a* wave on either the LV or LA tracings because of atrial fibrillation and loss of atrial contractions.

Abnormalities of diastolic pressure occur frequently in advanced cardiac diseases. The development of congestive heart failure is marked by an increase in the ventricular end-diastolic pressure in the affected ventricle(s),[8–11] regardless of whether heart failure results from myocardial contractile failure, severe volume overload, or diastolic impairment from myocardial or pericardial disease. An example of increased left ventricular end-diastolic pressure from a dog with myocardial failure caused by idiopathic dilated cardiomyopathy is shown in Figure 9–7*B*. The configuration of the diastolic ventricular and/or atrial pressure tracing may indicate the type of underlying abnormality. For example, atrioventricular valve regurgitation causes an increase in the mid-to-late systolic *v* wave in the corresponding atrium. Figures 9–6*C* and 9–7*C* demonstrate the increased end-diastolic pressure and increased *v* wave from dogs with marked tricuspid regurgitation and mitral regurgitation, respectively. Conditions that increase the resistance to ventricular filling cause an increased end-diastolic pressure and a predominantly increased atrial *a* wave. When this is caused by reduced ventricular compliance (increasing stiffness) due to myocardial hypertrophy, fibrosis, or infiltration, the left ventricle is often most affected, and the left ventricular diastolic pressure is usually greater than that in the right ventricle. When the filling restriction is caused by increased pericardial constraint (pericardial effusion or fibrosis), both ventricles are usually affected equally, and there are equivalent and synchronous increases in the diastolic pressures of both ventricles.[8–11, 22]

CARDIAC OUTPUT (FLOW) MEASUREMENT

The other primary hemodynamic variable measured during catheterization is blood flow, usually expressed as cardiac output (L/min) or cardiac index (L/min/kg or L/min/m²). The two most common methods used for flow measurement are oximetry and indicator dilution.[8–11]

OXIMETRY

Withdrawal of blood samples during cardiac catheterization is done primarily for determination of oxygen content (vol%, ml/dl and ml/L) or percent oxygen saturation.[8–11] These two measurements are directly related to the hemoglobin content of the blood by the following formula:

$$O_2 \text{ saturation } (\%) = \frac{O_2 \text{ content (ml } O_2\text{/dl blood)}}{\text{Hemoglobin (gmHb/dl blood)} \times 1.34 \text{ (ml } O_2\text{/gmHb)}}$$

The numerator is the measured oxygen content of the blood sample, while the denominator is the theoretical oxygen-carrying capacity of the sample based on the hemoglobin content and the oxygen-carrying capacity of normal hemoglobin. In practice, direct measurement of oxygen saturation is generally easier and faster than the methods used to determine oxygen content directly. Percent saturation may also be determined by measuring the partial pressure of oxygen (PO_2) in the sample and finding the corresponding point on the oxygen dissociation curve for hemoglobin. Samples for oximetry are collected from each chamber in heparinized syringes; air bubbles are expelled; syringes are capped and kept in an ice bath until analyzed.

Cardiac output can be determined by the *Fick principle,*[11] which states that if a measurable substance is continuously added to or removed from the blood by an organ, then the blood flow through the organ equals the amount of substance added or removed per unit of time, divided by the arteriovenous difference in the concentration of the substance. For measuring cardiac output, the organ is the lung and the substance added is oxygen. The A-V O_2 difference (ml O_2/dl blood) is found by measuring O_2 content of mixed venous blood sampled from the pulmonary artery (after mixing of the vena caval and coronary venous returns in the right atrium and ventricle) and systemic arterial blood (assumed to be similar to pulmonary venous O_2 content). Oxygen consumption (ml/min) is measured by comparing the O_2 content of the inspired air to that of a timed expired air sample collected through a spirometer into a collecting bag. Pulmonary blood flow (which in the absence of any shunts is equal to systemic flow or cardiac output) is then calculated by the Fick formula:

$$\text{Cardiac output (L/min)} = \frac{\text{Oxygen consumption (ml/min)}}{\begin{matrix}\text{Systemic arterial}\\ O_2 \text{ content (Vol\%)}\end{matrix} - \begin{matrix}\text{Pulmonary arterial}\\ O_2 \text{ content (Vol\%)}\end{matrix} \times 10}$$

A major drawback of the technique in animals is the necessity for the use of general anesthesia (which usually involves inhalation of gas, which is very high in O_2 content and completely saturates the blood and invalidates the method for practical use), and the cumbersome requirements for determining oxygen consumption.

The presence and magnitude of left-to-right or right-to-left shunts can also be determined by measuring the O_2 content or saturation in a series of samples drawn sequentially from the heart chambers and great vessels.[11] Normal pulmonary venous, left atrial and ventricular, and systemic arterial blood is highly saturated (approximately 95%) in the absence of significant pulmonary disease. In contrast, normal systemic venous, right atrial and ventricular, and pulmonary arterial blood is comparatively desaturated (70% to 80%). In most animals, the O_2 saturation of caudal vena caval blood is slightly higher than cranial vena caval blood, and mixing begins in the right atrium. Oxygen saturation is determined in blood samples from the cranial and caudal venae cavae, right atrium, right ventricle, and pulmonary artery. Because of incomplete mixing and the errors inherent in sampling and measurement, a difference of up to 3 percent cannot be considered significant. Any increase in O_2 saturation 5 percent or greater within the right heart chambers signifies a left-to-right shunt proximal to the sampling site. The location of the shunt is determined by the position of the step-up in saturation, and the magnitude of the shunt can be estimated (expressed as the pulmonary/systemic flow ratio Qp/Qs) directly by the size of the increase, using the following formula:

$$Qp/Qs = \frac{SaO_2 - MVO_2}{SaO_2 - PaO_2}$$

where SaO_2, Pa_2, and MVO_2 are the systemic arterial, pulmonary artery, and mixed venous (right atrium or venae cavae) oxygen contents or saturations, respectively. In similar fashion, left ventricular, ascending, and descending aortic blood oxygen content or saturation can detect a right-to-left shunt by a fall in saturation somewhere along the path of the normally highly saturated (≥95%) arterial blood. Because of the requirement for a 5 percent or greater change in O_2 content or saturation to detect a shunt, this method is only effective in detecting shunts of at least 20 percent of the systemic (left-to-right) or pulmonary (right-to-left) flow. In animals, the method is useful only if the patient is breathing room air, a drawback to its routine clinical use in anesthetized patients.

INDICATOR DILUTION

The principle of indicator (dye) dilution is an adaptation of the Fick principle.[11] In this technique, an external indicator substance is injected into the flowing blood upstream, and its concentration is continuously measured downstream. If the amount of indicator injected is known and its average concentration as it passes the sampling site can be determined, the rate of blood flow can be calculated. In equation form the relationship is

$$\text{Q (flow rate)} = \frac{\text{I (quantity of indicator injected)}}{\text{C (mean concentration)} \times \text{t (passage time)}}$$

By injecting the indicator into the systemic venous blood (usually the right atrium) and sampling downstream from the heart (usually the pulmonary artery

or a peripheral artery), cardiac output can be obtained.

A number of different indicators and sampling systems have been employed, including photometric detection of various dyes, electrode detection of hydrogen or concentrated saline, and thermistor detection of cold solute. The requirements for a successful indicator substance are: (1) it should be nontoxic, nonmetabolized, readily injected and completely miscible with blood; (2) it should mix completely and uniformly with the blood prior to sampling; (3) it should not be added to or subtracted from the blood during initial passage between the injection and sampling sites; and (4) it must be easily and rapidly detected by a downstream detecting device. This usually requires at least one mixing chamber (ventricle) between injection and sampling sites.

Prior to the 1980s the most commonly employed indicator was indocyanine green dye measured by a photometric densitometer. Today the most common system is thermodilution, which uses cold saline or dextrose as the indicator and a thermistor (a material whose resistance varies with temperature) as the detector. Although the methodology is somewhat different, the principles are the same for each system.[8–11]

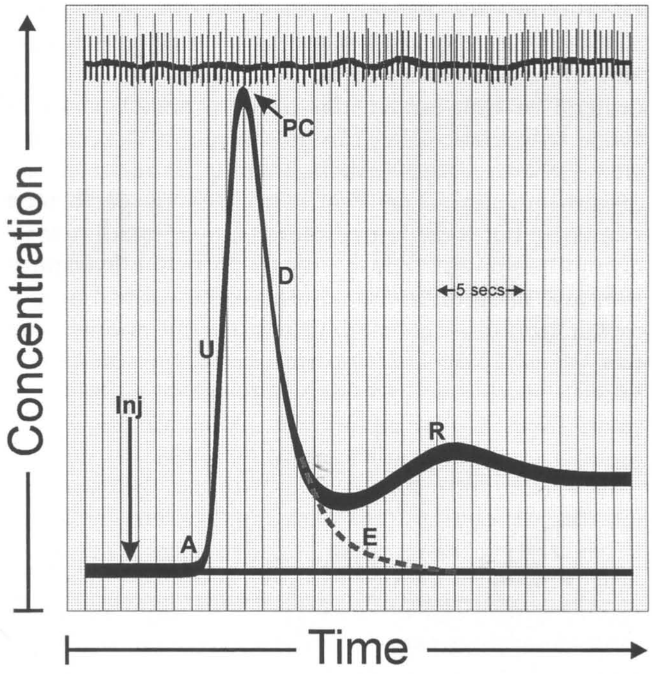


FIGURE 9–8

Normal indicator dilution curve recorded following injection of indocyanine green dye into the right atrium and continuous withdrawal of blood from the femoral artery. The deflection height represents the concentration of green dye in the blood passing the sampling site during the time following injection. The typical curve is characterized by a delay prior to the initial appearance of the dye *(A)*, a rapid upstroke *(U)* to a peak concentration *(PC)*, and an exponential downslope *(D)* interrupted by recirculation *(R)*. To complete the primary curve, the downslope is extrapolated *(E)*, assuming continued exponential disappearance. The area under the primary curve is used to compute cardiac output. Thermodilution curves appear similar except that the exponential downslope continues to the baseline without a recirculation phase.

INDOCYANINE GREEN DYE DILUTION. The injection site is usually the vena cava or right atrium. The sampling site is usually the aorta or a more peripheral artery. The arterial catheter is connected to a densitometric cuvette whose filter provides light in the wavelength range of the dye's peak spectral absorption (800 mμ). This is connected to a constant-rate withdrawal pump. The pump is started, and as blood is drawn through the cuvette, a baseline (representing the light transmission through the blood) is obtained. A known amount of freshly prepared green dye is injected as a bolus into the venous catheter. After a short delay (the appearance time) a curve, representing the reduction in light transmission through the blood due to absorption by the dye, is inscribed with a typical rapid upstroke to a peak (build-up time), exponential downslope, and recirculation with gradual return toward the baseline (Fig. 9–8). After inscription of the curve, the withdrawn blood can be re-infused. The curve is calibrated by serially drawing dye samples of known concentration through the densitometer cuvette to correlate deflection height in millimeters to concentration in mg/ml. Today the process of calibration, extrapolation of the downslope of the primary curve, and measurement of the mean concentration (area under the primary curve) are performed automatically by a small computer. The major drawback of this technique in small animals is the necessity of withdrawing significant volumes of blood through the densitometer cuvette, which is hazardous in very small patients and also may significantly alter the hemodynamics that are under study.

THERMODILUTION. This method uses a multilumen catheter with three ports connected to a distal end hole (positioned in the pulmonary artery), a proximal side hole (positioned in the right atrium), and the balloon tip, and an electrical connection to a sampling thermistor near the tip (also in the pulmonary artery). A known volume and temperature of iced saline or dextrose (usually 3 to 5 ml) is injected into the right atrium through the proximal port and sampled by the thermistor in the pulmonary artery. The inscribed curve is similar to that for indocyanine green dye (Fig. 9–8), except that the temperature indicator is rapidly lost during peripheral vascular transit, and there is no recirculation portion of the curve. The advantages of thermodilution include its safety, rapid return to baseline, and lack of indicator build-up during the study, allowing for rapid repetition of as many injections as needed.

Cardiac output is determined from the inscribed

curve as follows: from the formula shown earlier, output is calculated from the amount of indicator injected and the curve area. The denominator is, in fact, the integral or area under the primary curve, which is found by extrapolating the downslope of the primary curve to correct the inscribed curve for recirculation of the indicator (Fig. 9–9). This may be performed manually, but today most studies use compact cardiac output computers that rapidly perform the extrapolation and integration and compute the cardiac output within seconds. The method is useful in animals and can be used regardless of the type of anesthesia employed. Since blood withdrawal is not required, thermodilution may be adapted and used on very small animals with comparative safety.

Indicator dilution may also be used to identify intracardiac and extracardiac shunts in patients with congenital heart disease[11] (Fig. 9–9). By selecting appropriate injection and sampling sites, both left-to-right and right-to-left shunts may be detected and localized. Using an aortic or peripheral arterial sampling site, any right heart chamber injection should appear after a delay of 3 to 5 seconds. Early appearance of the indicator, recorded as a premature rise on the inscribed curve prior to the primary curve, indicates a right-to-left shunt distal to the injection site (Fig. 9–9, *top*). The shunt can be localized by recording a series of curves during successively more distal injection sites (right atrium, right ventricular inflow region, right ventricular outflow region, main pulmonary artery,

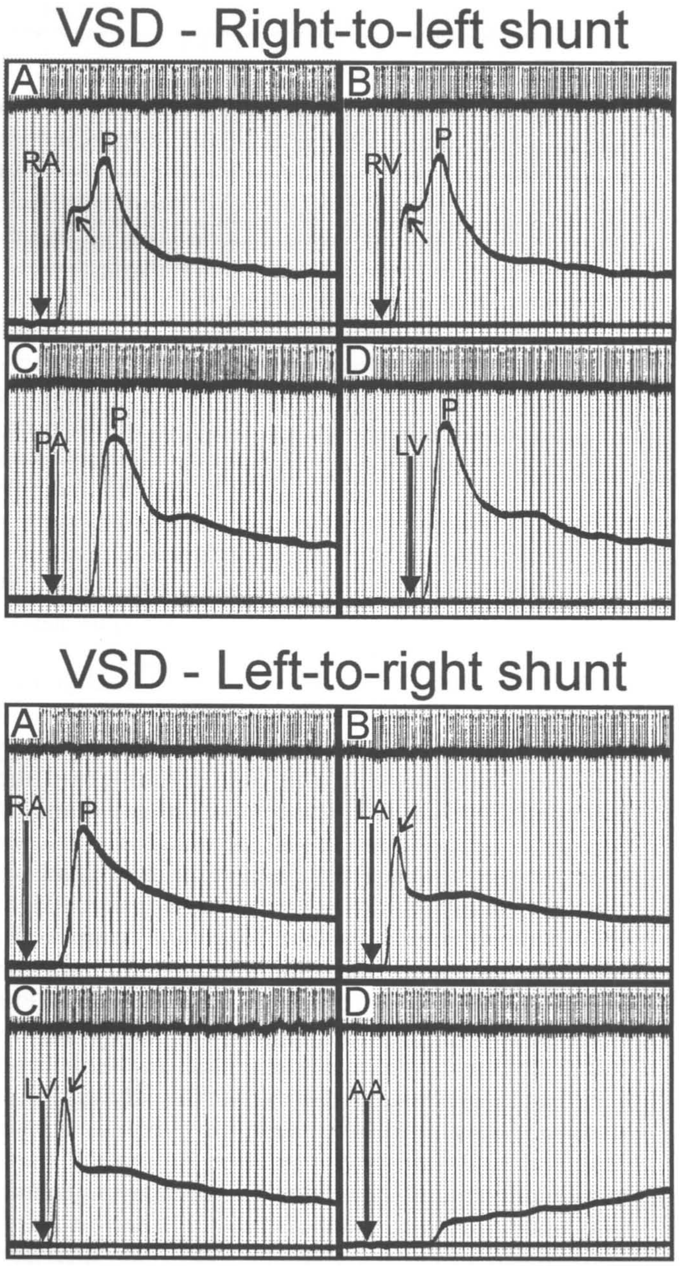


FIGURE 9–9

Abnormal indicator dilution curves. *Top:* Curves recorded from a sampling site in the descending aorta after injection of dye at the indicated sites in a dog with a *right-to-left* shunting ventricular septal defect. (A–C) The dye appears prematurely *(small arrows)* prior to the primary curve *(P)* after right atrium *(RA)* and right ventricle *(RV)* injection, but not after pulmonary artery *(PA)* injection, localizing the shunt to the ventricular level. (D) Dye appears normally and quickly after left ventricle *(LV)* injection. *Bottom:* Curves recorded from a dog with a *left-to-right* shunting ventricular septal defect. (A) After RA injection, the dye appears after a normal appearance time, inscribing the primary curve. The prolonged, gradual downslope without a separate recirculation phase is due to early recirculation of dye passing through the shunt and reappearing sooner at the arterial sampling site. (B–D) These curves were recorded by sampling from the pulmonary artery following injection of dye at the indicated sites. Dye appears prematurely in the PA after left atrium *(LA)* and LV injection but not after ascending aorta *(AA)*, localizing the shunt to the ventricular level.

and distal pulmonary artery) until the dye no longer appears prematurely when the injection site is distal to the shunt. Detection of left-to-right shunts is more problematic using venous injection and aortic sampling sites. The resulting curve shows a somewhat lower peak deflection and a prolonged, gradual disappearance slope due to early recirculation of dye through the shunt (Fig. 9–9, *bottom, A*). Unfortunately, patients with low cardiac output (e.g., heart failure) or moderate valvular insufficiency (e.g., mitral regurgitation) may also have venous dye curves with low peaks and prolonged, gradual downslopes. Localization of the shunt is also more difficult, requiring sampling in a pulmonary artery branch for premature indicator appearance after successive injections into the left atrium, left ventricle, and aortic root (Fig. 9–9, *bottom*).

Both oximetry and indicator dilution are still used in human cardiac catheterization laboratories for cardiac output determination, and oximetry is still used to help quantify shunts. In small animal practice today, left-to-right and right-to-left shunts are most often identified and localized by Doppler echocardiography and contrast echocardiography, respectively (chapter 8).

ANGIOCARDIOGRAPHY

Angiography of the heart and great vessels has been used on literally millions of humans with cardiovascular disease over the past 30 to 40 years and is still considered to be the gold standard for many cardiac diagnoses[1, 8–10] (although angiography is slowly being replaced by echo-Doppler imaging and other imaging modalities for many conditions). Compared with the paucity of clinical reports of hemodynamic measurements in dogs and cats, there have been numerous reports of angiographic studies in normal experimental animals and patients with congenital and acquired heart diseases.[23–33] Angiocardiography is the most common imaging study performed during cardiac catheterization. It involves the injection of liquid radiographic contrast material into the blood stream to opacify the blood and examine flow dynamics in the heart and great vessels. The resulting image is monitored by fluoroscopy and recorded on videotape, on 16-mm cine (movie) film, or on a series of small x-ray films. Although it is possible to record a few films by manual film changing through a homemade tunnel,[34] superior quality studies are obtained using a programmable rapid film changer that can record 1 to 6 films per second. Contrast injections may be performed by hand (especially in very small animals) or using an automated power injector whose pressure and/or injection rate can be programmed.

CONTRAST AGENTS. All the available injectable radiographic contrast agents used for angiography contain iodine as the x-ray absorbing element, and they are divided into *ionic agents* and *non-ionic agents*, based on their behavior in solution.[8–10, 35, 36] The older ionic agents (e.g., Renografin, Hypaque, and Angiovist) often use diatrizoate as the anionic iodine carrier and couple this with cationic sodium and meglumine. The newer non-ionic agents (e.g., Omnipaque, Isovue, Optiray) do not ionize in solution and provide a higher concentration of iodine per volume and a lower osmolality than the ionic agents. However, they are also significantly more costly than the ionic products. All agents provide good to excellent cardiovascular contrast in the heart and blood vessels.

Adverse effects of intravascular contrast include vasodilation (hypotension), arrhythmias, increased thrombosis, and nephrotoxicity; most appear to be directly correlated with the contrast agent's osmolality.[9] The principal advantage of the non-ionic agents lies in their lower osmolality and reduced side effects. Despite this advantage, the ionic agents have a good safety record and are still used in many patients with stable heart disease. The non-ionic agents should be considered for use in higher-risk patients (myocardial failure, pulmonary hypertension, unstable hemodynamics) and in any patient that experiences a severe adverse reaction to an ionic agent.

CARDIAC ANGIOGRAMS

NONSELECTIVE ANGIOGRAPHY

This is performed by peripheral venous injection of contrast, which then successively opacifies the vena cava, right atrium, right ventricle, pulmonary arteries and veins, left atrium, left ventricle, and aorta. The technique is simpler than selective injections, requiring only a peripheral venous catheter.[25, 26, 29, 30] It was used extensively in the 1970s to differentiate the major types of feline myocardial diseases.[23, 24, 30] The main disadvantages are

(1) overlap of opacified structures often makes examination of individual structures difficult, and
(2) the contrast is diluted as it progresses through the circulation, resulting in poorer opacification of the left side of the heart in some cases, especially when circulation time is prolonged.

SELECTIVE ANGIOGRAPHY

This implies contrast injection at specific sites designed to optimize the opacification of specific structures or to demonstrate flow abnormalities. Examples

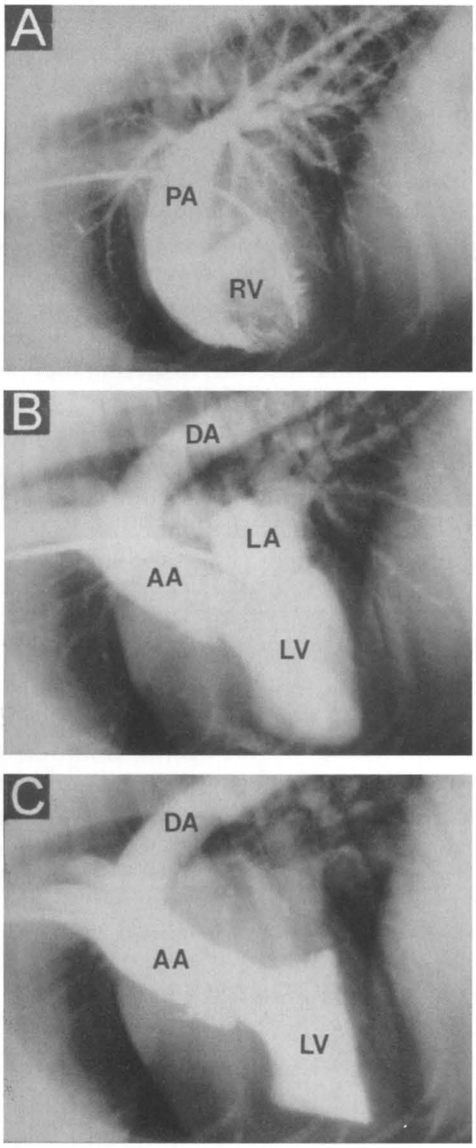


FIGURE 9–10

Angiocardiography in the normal dog. (A) Right ventricular injection outlines the right ventricle *(RV)*, main pulmonary artery *(PA)*, and its branches. (B) Left-sided heart phase of the RV injection shown in (A) outlines the left atrium *(LA)*, left ventricle *(LV)*, ascending aorta *(AA)*, and descending aorta *(DA)*. (C) Left ventricular injection outlines the LV and aorta and its cranial branches.

of normal right- and left-sided heart angiograms are illustrated in Figures 9–10, 9–11; Figures 24–3, 24–4, 24–8, 24–10, 24–22, 24–32, 24–34, 24–41, 24–50, 24–53, and 24–59.

Choice of selective injection site(s) in any patient should be based on what specific anatomic or flow abnormality one is attempting to demonstrate, on the patient's overall condition and estimated risk of catheterization and angiography, and by figuring which injection site(s) and view(s) will provide the greatest diagnostic information in the least amount of time. The following principles apply to injection site selection in animals with cardiac disease:

1. To demonstrate valvular regurgitation, the injection should be made in the downstream chamber or vessel adjacent to the affected valve;
2. To demonstrate an obstructive/stenotic lesion, the injection should be made in the upstream chamber or vessel adjacent to the obstructed area;
3. To demonstrate a shunting lesion, the injection should be made in the upstream chamber or vessel adjacent to the defect;
4. Contrast outlining of abnormalities may be satisfactory using nonselective angiography, but optimum opacification generally requires injection as close to the abnormality as possible.

To illustrate these points, examples of selective angiograms of various congenital heart defects are shown in Figure 9–12.

Although catheterization and angiography have most often been applied to the diagnosis of congenital heart disease in animals, angiography has also been used to help diagnose and evaluate many other conditions, including left ventricular volume overload;[31–33]

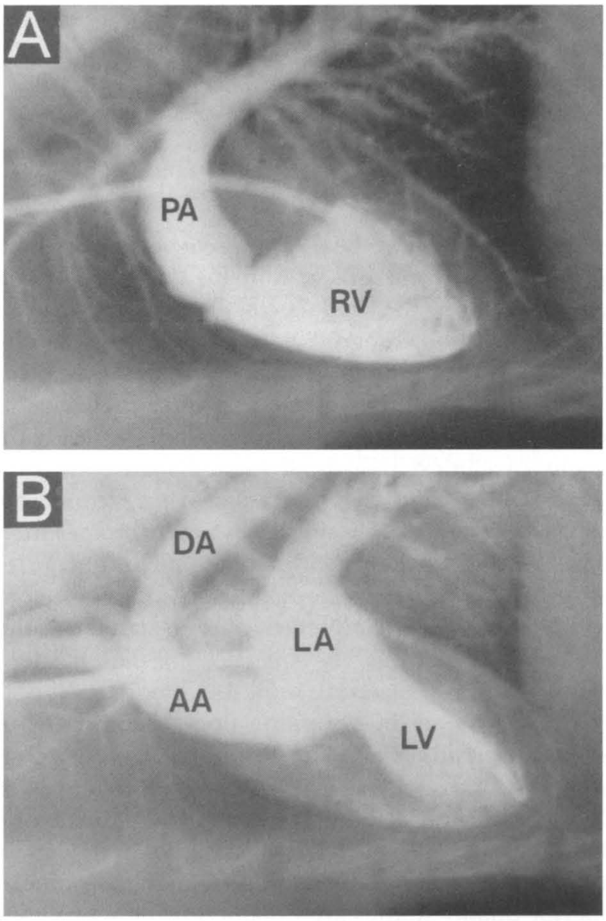


FIGURE 9–11

Angiocardiography in a normal cat. (A) Right ventricular injection outlines the right ventricle *(RV)* and pulmonary artery *(PA)*. (B) Left-sided heart phase of the RV injection shown in (A) outlines the left atrium *(LA)* and associated pulmonary veins, left ventricle *(LV)*, ascending aorta *(AA)*, and descending aorta *(DA)*.

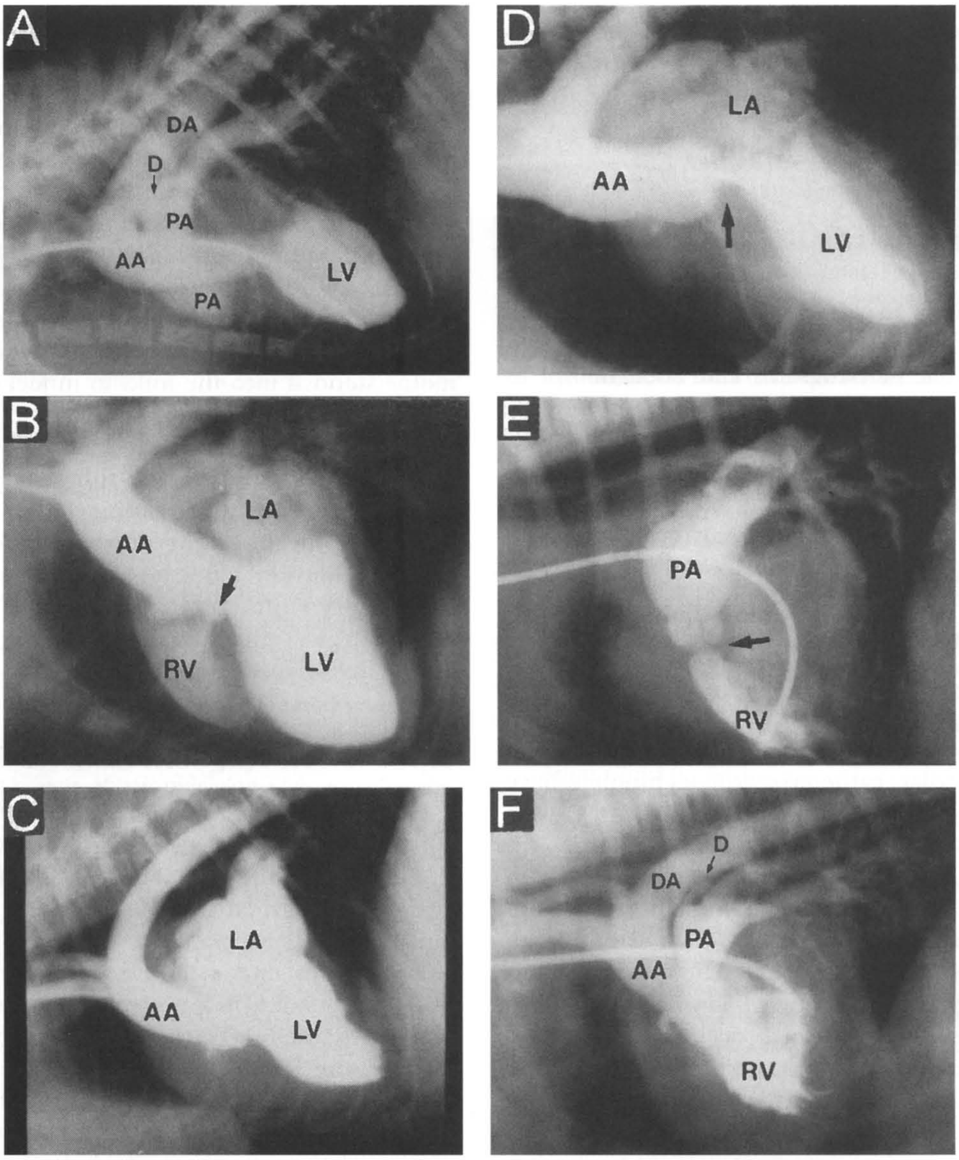


FIGURE 9–12

Examples of angiocardiographic abnormalities (compare with normal studies shown in Figures 9–10 and 9–11). (A) LV injection: Patent ductus arteriosus (PDA) in a cat. The PDA *(arrow)* connects the descending aorta to the pulmonary artery, allowing a left-to-right shunt and opacification of the pulmonary artery in addition to the left-sided heart. (B) LV injection: Small ventricular septal defect (VSD) in a dog. The VSD *(arrow)*, which is just below the aortic valve, shunts contrast into the RV outflow region and causes variable distortion of the root of the aorta. The left ventricle is mildly dilated and there is mild mitral regurgitation, which partially opacifies the left atrium. (C) LV injection: Congenital mitral valve dysplasia in a dog. In addition to outlining the LV and aorta, there is dilatation and marked opacification of the left atrium due to severe mitral regurgitation. (D) LV injection: Congenital subaortic stenosis in a dog. The obstruction *(arrow)* is located just below the aortic valve, and there is mild poststenotic dilatation of the ascending aorta. Mild mitral regurgitation is partially opacifying the left atrium. (E) RV injection: Congenital pulmonic stenosis in a dog. The obstruction *(arrow)* is located just below the pulmonic valve, whose leaflets are barely visible above the stenosis. The RV is thickened, and there is poststenotic dilatation of the main pulmonary artery. (F) RV injection: Tetralogy of Fallot in a dog. The RV is thickened and both the aorta and pulmonary artery are simultaneously opacified, indicating a right-to-left shunt at the ventricular level. The LV is not distinguishable, but the aortic root is wide and appears displaced somewhat ventrally in this view. Although pulmonic stenosis is not visible on this frame, there is slight poststenotic dilatation of the main pulmonary artery. There is an incidental finding of a very small patent ductus arteriosus *(arrow)*. AA, ascending aorta; D, patent ductus arteriosus; DA, descending aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

heartworm disease[21] and other types of pulmonary thromboembolism;[37] heart base tumors;[38] intracardiac tumors;[39] and a variety of extracardiac vascular abnormalities.[40–42]

ELECTROPHYSIOLOGIC TECHNIQUES

Direct recording of cardiac electrical signals is well established, but the use of multielectrode catheters to record intracardiac electrograms and also attempt to ablate a region of electrical instability is quite new. By mapping multiple electrograms in a heart chamber, the point of origin of an arrhythmia may be identified and, in some cases, ablated using electrical, laser, or heat energy at the catheter tip. Currently, very few clinical electrophysiologic studies of this type have been reported in animals.[43]

INTERVENTIONAL TECHNIQUES

Diagnostic cardiac catheterization techniques have been clinically used in humans since the early 1950s and in animals since the early 1960s.[1–3] Starting in the early 1980s, interventional techniques have been increasingly used along with conventional methods in human and animal catheterization laboratories to attempt to treat certain disorders.[8–10] The most common of these techniques are balloon dilation angioplasty or valvuloplasty, transcatheter coil occlusion of persistently patent ductus arteriosus, and catheter ablation of arrhythmogenic endomyocardial regions (described earlier). These procedures provide significant cost savings over some surgical interventions, and advancements in device technology and delivery methodologies should make these techniques more attractive in the future.

BALLOON DILATION (VALVULOPLASTY)

The technique of balloon dilation has been applied to a variety of obstructive lesions in humans, especially adults with coronary obstructions and children with congenital cardiac or vascular obstructions.[8, 9] In animals, it has been used primarily as a treatment for canine congenital cardiac obstructions, especially pulmonic stenosis, with encouraging results.[44, 45] It has also been employed to attempt to dilate congenital subaortic stenosis in dogs, but the results have been discouraging.[46]

Balloon valvuloplasty of congenital valvular pulmonic stenosis is accomplished by advancing an end-hole catheter from the jugular vein or femoral vein through the right ventricle and past the obstruction into the pulmonary artery. A sturdy, J-tipped guidewire is passed through this catheter and out into the lung; the catheter is then removed, leaving the wire in place. The balloon dilation catheter is then inserted over the guidewire and carefully directed through the heart until the balloon is positioned across the obstruction. The dilating balloon is then inflated one to three times with a 5:1 solution of saline or dextrose and contrast (see Fig. 24–23). The procedure is monitored throughout by fluoroscopy and ECG. Results to date have indicated moderate success in reducing severe pulmonic stenosis into the mild to moderate range. With valvular stenosis, severe complications have been uncommon. However, extreme caution is advised in attempting to dilate dogs with subvalvular pulmonic stenosis caused by an aberrant left coronary artery arising from the right coronary (see Fig. 24–3). Balloon dilation has caused fatalities due to coronary artery rupture in such animals,[45] and in these cases, surgical alternative treatments should probably be investigated.

TRANSCATHETER COIL OCCLUSION

Procedures for transcatheter coil occlusion, used most commonly to close patent ductus arteriosus, are gaining increasing popularity over standard surgical ligation.[47–49] Several techniques have been advocated for inserting spring-loaded Gianturco coils into the patent ductus under fluoroscopic guidance (see Fig. 24–46). An initial popular method directs a delivery catheter (containing a coil loaded into its distal end) through the femoral artery up the descending aorta, and crosses the patent ductus from the aortic side. The coil is then extruded with the aim of placing the initial loop on the pulmonary arterial end, thus anchoring the remaining loops, which are deployed on the ductal ampula. A modification of this technique using a preformed nitinol snare to provide controlled coil delivery and prevent coil embolization involves passing a snare catheter through femoral venous access into the right side of the heart and into the pulmonary artery side of the ductus; "grabbing" the initial extruded loop from the delivery catheter as previously described; and assuring optimal coil positioning prior to withdrawing the catheters.[50] These techniques should improve as enhancements in manufactured devices become available.

REFERENCES

1. Braunwald E, Gorlin R, McIntosh HD, et al. Cooperative study on cardiac catheterization. Summary. Circulation 37 (5 Suppl): III93, 1968

2. Wallace C. Cardiac catheterization to aid in diagnosis of cardiovascular disease. Small Anim Clin 2:232, 1962
3. Ettinger SJ, Suter PF. Canine Cardiology. Philadelphia, WB Saunders, 1970, p 170
4. Noble WH, Kay JC. Cardiac catheterization in dogs. Can Anaesth Soc J 21:616, 1974
5. Knight DH. Principles of Cardiac Catheterization. *In* Kirk RW (ed): Current Veterinary Therapy V. Philadelphia, WB Saunders, 1974, p 251
6. Wood GL, Suter PF. Principles of cardiac catheterization. *In* Kirk RW (ed): Current Veterinary Therapy VI. Philadelphia, WB Saunders, 1977, p 323
7. Lubell DL. The Cath Lab. An Introduction. Philadelphia, Lea & Febiger, 1990
8. Grossman W, Baim DS. Cardiac Catheterization, Angiography and Intervention. 4th ed. Philadelphia, Lea & Febiger, 1991
9. Pepine CJ, Hill JA, Lambert CR (eds): Diagnostic and Therapeutic Cardiac Catheterization. 2nd ed. Baltimore, Williams & Wilkins, 1994
10. Davidson CJ, Fishman RF, Bonow RO. Cardiac catheterization. *In* Braunwald E (ed): Heart Disease. A Textbook of Cardiovascular Medicine. 5th ed. Philadelphia, WB Saunders, 1997, p 177
11. Yang SS, Bentivoglio LG, Maranhao V, Goldberg H. From Cardiac Catheterization Data to Hemodynamic Parameters. 3rd ed. Philadelphia, FA Davis, 1988
12. Lemke KA, Tranquilli WJ, Thurmon JC, Olson WA. The hemodynamic effects of atropine and glycopyrrolate in isoflurane-xylazine anesthetized dogs. Vet Surg 21:82, 1992
13. Thurmon JC, Tranquilli WJ, Benson GJ (eds): Lumb & Jones Veterinary Anesthesia. 3rd ed. Baltimore, Williams & Wilkins, 1996
14. Muir WW III. Handbook of Veterinary Anesthesia. 2nd ed. St. Louis, CV Mosby, 1995
15. Wyman RM, Safian RD, Portway V, et al. Current complications of diagnostic and therapeutic cardiac catheterization. J Am Coll Cardiol 12:1400, 1988
16. Buchanan JW, Pyle RL. Cardiac tamponade during catheterization of a dog with congenital heart disease. J Am Vet Med Assoc 149:1056, 1966
17. Robertson SA, Fowler DA. A complication of cardiac catheterization in the dog. Vet Radiol 29:202, 1988
18. Fingland RB, Bonagura JD, Myer CW. Pulmonic stenosis in the dog: 29 cases (1975–1984). J Am Vet Med Assoc 189:218, 1986
19. Lehmkuhl LB, Bonagura JD, Stepien RL, Jones DE. Comparison of pressure gradients determined by Doppler echocardiography and cardiac catheterization in dogs with subaortic stenosis. (Abstract). J Vet Intern Med 6:113, 1992
20. Brown WA, Thomas WP. Balloon valvuloplasty of tricuspid stenosis in a Labrador retriever. J Vet Intern Med 9:419, 1995
21. Knight DH. Evolution of pulmonary artery disease in canine dirofilariasis: evaluation by blood pressure measurements and angiography. Proceedings, Heartworm Symposium, 1980. Veterinary Medicine Publishing Company, Edwardsville, KS, 1981, p 55
22. Thomas WP, Reed JR, Bauer TG, Breznock EM. Constrictive pericardial disease in the dog. J Am Vet Med Assoc 184:546, 1984
23. Wise M. Non-selective angiocardiography in the normal dog and cat. Vet Radiol 23:144, 1982
24. Owens JM, Twedt DC. Non-selective angiocardiography in the cat. Vet Clin North Am 7:309, 1977
25. Buchanan JW. Selective angiography and angiocardiography in dogs with acquired cardiovascular disease. J Am Vet Radiol Soc 6:5, 1965
26. Buchanan JW, Patterson DF. Selective angiography and angiocardiography in dogs with congenital cardiovascular disease. J Am Vet Radiol Soc 6:21, 1965
27. Knauer KW. Angiocardiography in acquired heart disease. J Am Anim Hosp Assoc 8:308, 1972
28. Pyle RL. Angiocardiography in congenital cardiovascular diseases of the dog. J Am Anim Hosp Assoc 8:310, 1972
29. Stickle RL, Anderson LK. Diagnosis of common congenital heart anomalies in the dog using survey and nonselective contrast radiography. Vet Radiol 28:6, 1987
30. Fox PR, Bond BR. Non-selective and selective angiocardiography. Vet Clin North Am Small Anim Pract 13:259, 1983
31. Lord PF. Left ventricular volumes of diseased canine heart: Congestive cardiomyopathy and volume overload (patent ductus arteriosus and primary mitral valvular insufficiency). Am J Vet Res 35:493, 1974
32. Barlte SH, Sanmarco ME. Measurement of left ventricular volume by biplane angiocardiography and indicator washout techniques: a comparison in the canine heart. Circ Res 19:295, 1966
33. Bentivoglio LG, Cuesta AJ, Griffith LD, Geczy M. Evaluation of single plane angiography for left ventricular volume in the intact dog. Cardiovasc Res 10:283, 1976
34. Patterson DF, Botts RP. A simple cassette changer. Small Anim Clin 1:1, 1961
35. Frech RS. Toxicity studies of coronary arteriographic media in dogs. Invest Radiol 10:323, 1975
36. Nakamura H, Kurata M, Haruta K. Effects of ionic and nonionic contrast media on cardiohemodynamics and quality of radiographic image during canine angiography. J Vet Med Sci 56:91, 1994
37. Koblik PD, Hornof W, Harnagel SH, Fisher PE. A comparison of pulmonary angiography, digital subtraction, and ^{99m}Tc-DTPA/MAA ventilation-perfusion scintigraphy for detection of experimental pulmonary emboli in the dog. Vet Radiol 30:159, 1989
38. Cantwell HD, Blevins WE, Weirich WE. Angiographic diagnosis of heartbase tumor in the dog. J Am Anim Hosp Assoc 18:83, 1982
39. Bright JM, Toal RL, Blackford LM. Right ventricular outflow obstruction caused by primary cardiac neoplasia. J Vet Intern Med 4:12, 1990
40. Suter PF. Portal vein anomalies in the dog: their angiographic diagnosis. J Am Vet Radiol Soc 16:84, 1990
41. Gomez JA, Lawson TL, Korobkin M, Moss AA. Selective abdominal angiography in the dog. J Am Vet Radiol Soc 14:72, 1973
42. van Bree H, de Rick A, Mattheews D. Angiographic features in a case of extensive arterial thrombosis in a dog. J Small Anim Pract 22:641, 1981
43. Wright KN, Atkins CE, Kanter R. Supraventricular tachycardia in four young dogs. J Am Vet Med Assoc 208:75, 1996
44. deMadron E, Bussadori C. Five cases of valvuloplasty with a balloon catheter for stenotic pulmonary valves in dogs. Prat Med Chir Anim Comp 29:383, 1994
45. Kittleson M, Thomas W, Loyer C, Kienle R. Letter to the editor [Pulmonic stenosis and balloon valvuloplasty in dogs]. J Vet Intern Med 6:250, 1992
46. deLellis LA, Thomas WP, Pion PD. Balloon dilation of congenital subaortic stenosis in the dog. J Vet Intern Med 7:1532, 1993
47. Schneider M, Hagel K-J, Schneider I, Neu H. Transvenös Coil-Embolisation zum Verschluss des persistierenden

Ductus arteriosus (Botalli) bei einem Hund. Kleintierpraxis 41:685, 1996
48. Hijazi ZM, Lloyd TR, Beekman RH, et al. Transcatheter closure with single or multiple Gianturco coils of patent ductus arteriosus in infants weighing ≤ 8 kg: retrograde versus antegrade approach. Am Heart J 132:827, 1996
49. Miller MW, Bonagura JD, Meurs KM, et al. Percutaneous catheter occlusion of patent ductus arteriosus. Proceedings, 13th Annual ACVIM Forum, 1995, p 308
50. Fox PR, Bond BR, Sommer RJ. Nonsurgical transcatheter coil occlusion of patent ductus arteriosus in two dogs using a preformed nitinol snare delivery technique. J Vet Int Med 12:182, 1998

10

Nuclear Imaging, Computed Tomography, and Magnetic Resonance Imaging of the Heart

GREGORY B. DANIEL
JANICE M. BRIGHT

SPECIALIZED IMAGING TECHNIQUES

Nuclear scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI) are specialized imaging techniques that may be useful to evaluate certain cardiovascular disorders. Currently, they are available only at large referral institutions because of their expense and required technical expertise. Familiarity with their potential application and utility will help identify cases that would benefit from their use.

Nuclear scintigraphy is particularly suited to detecting and quantifying intracardiac or vascular shunts; evaluating ventricular function; mapping myocardial perfusion; and evaluating obstructions to systemic and pulmonary blood flow. Computed tomography and MRI have several important advantages over echocardiographic imaging through superior imaging of the great vessels, pericardium, and mediastinum. Thus, CT and MRI are particularly helpful for evaluating intrathoracic and cardiac masses, diseases of the pericardium, and complex congenital heart defects.

NUCLEAR CARDIOLOGY

Applications of nuclear cardiology have been growing in clinical practice and research.[1] They are relatively quick to conduct, require only intravenous injections of a gamma ray–emitting radiopharmaceutical, and do not require anesthesia. Most cardiac studies are performed using a gamma camera interfaced with a dedicated imaging computer. The gamma camera consists of a collimator that filters the gamma rays emitted from the patient; a large

sodium iodide crystal that converts the gamma rays into light; and an array of photomultiplier tubes that translate tiny bursts of light into voltage signals. The computer acquires, processes, and stores the imaging data so that they can be subsequently mapped on a display monitor.

EVALUATION OF CARDIAC SHUNTS

The direction and magnitude of congenital cardiac shunts are easily determined using first-pass radionuclide angiocardiography (FPRA), which records the passage of a radioactive bolus through the central circulation as a series of sequential images.[1a, 2] Any radiopharmaceutical that freely passes through the pulmonary capillary beds can be used for shunt analysis, but pertechnetate ($^{99m}TcO_4^-$) is the most commonly used agent. A small volume (0.5 to 1.0 ml) is injected rapidly to ensure delivery of a concentrated bolus of activity and ensure that the cardiac chambers are temporally resolved. The animal is positioned in lateral recumbency over the gamma camera, and a dynamic acquisition (i.e., a series of sequential images obtained by the computer), with a frame rate of 2 to 4 frames per second for 30 to 40 seconds, is initiated upon injection of the radiopharmaceutical.

A normal FPRA is characterized by passage of the radiopharmaceutical sequentially through the cranial vena cava, right atrium, right ventricle, pulmonary arteries, lung, pulmonary veins, left atrium, left ventricle, and finally the aorta (Fig. 10–1).[1a, 2]

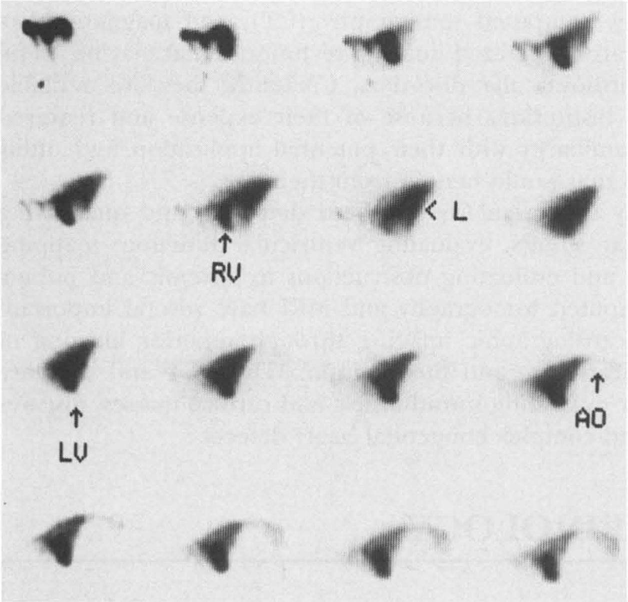


FIGURE 10–1

First-pass radionuclide angiocardiogram in a normal dog, recorded at 2 frames/sec. Dorsal is at the top of the image. The dog's head is to the left. Initial image *(top left)* shows the majority of the radioactive bolus in the cranial vena cava following a cephalic vein injection. The right ventricle *(RV)*, lung *(L)*, left ventricle *(LV)* and abdominal aorta *(AO)* appear in normal sequence.

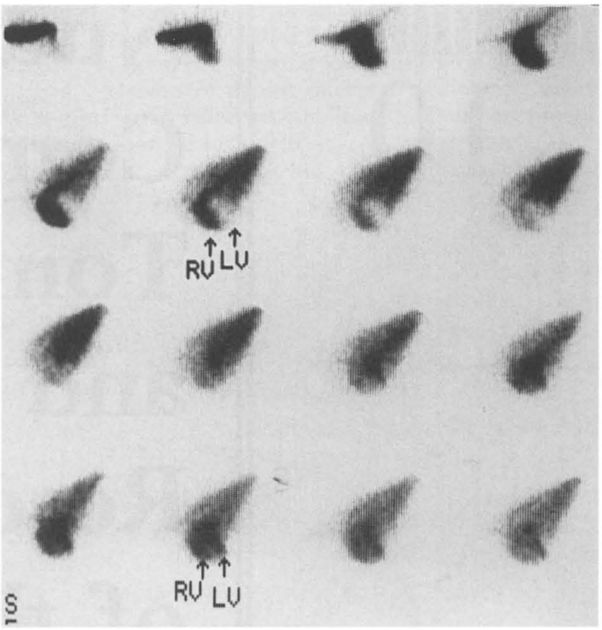


FIGURE 10–2

First-pass radionuclide angiocardiogram of a dog with a ventricular septal defect *(VSD)*. The animal's orientation and the image frame rate are the same as in Figure 10–1. Pulmonary activity is prolonged due to recirculation of blood. Note the reappearance of the right ventricle *(RV)* during the levophase. LV, left ventricle.

LEFT-TO-RIGHT SHUNTS

Analysis of the FPRA begins with visual inspection of the sequential images displayed on the computer screen in cinematic motion. Left-to-right shunts are characterized by prolonged retention of radioactivity in the lung due to immediate recirculation of blood through the pulmonary vasculature. The anatomic location of the shunt cannot always be determined by FPRA. Occasionally, a ventricular septal defect is identifiable as the radioactive bolus passes from the left ventricle directly into the right ventricle during the levophase (Fig. 10–2).[1a] The method is useful for determining shunt size when surgery is contemplated.

In the normal animal, activity in the lung peaks then rapidly decreases to a low level as the pertechnetate bolus passes through the pulmonary vasculature. Residual activity in the lung following initial passage of bolus represents systemic arterial blood supply to the lung as well as superimposed thoracic wall activity.[1a, 2–4]

In animals with a left-to-right shunt, the pulmonary time activity curve evidences a second peak and a substantially delayed washout phase as the pertechnetate bolus continuously recirculates through the shunting defect (Fig. 10–3). Because the area under

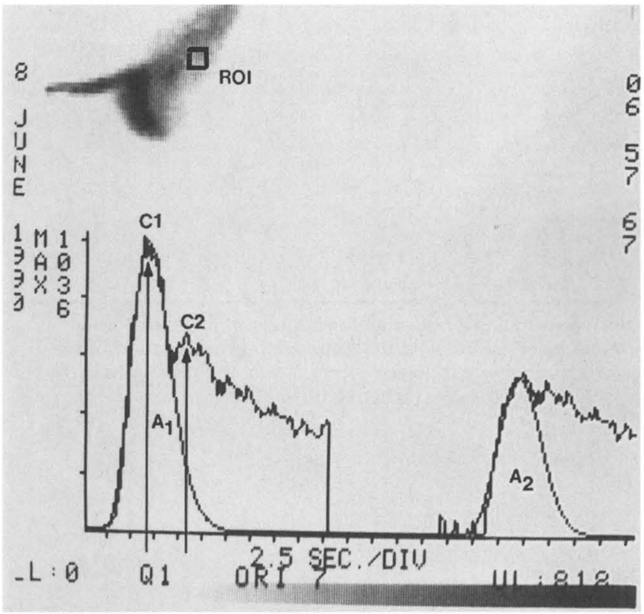


FIGURE 10–3

Evaluation of the magnitude of a left-to-right shunt in an animal with a ventricular septal defect *(VSD)* obtained from a first-pass radionuclide angiocardiogram. First, a composite image of the thorax is made by summing the image frames. Next, a region of interest *(ROI)* is drawn over the dorsal caudal lung fields, carefully excluding areas over the heart and aorta. The amount of radioactivity (counts) in this ROI is then plotted as a function of time to generate a time activity curve. The lung time activity curve *(A_1)* represents a gamma variate fit to the lung peak of the time activity curve. The second curve *(A_2)*, representing the gamma variate fit of the recirculation peak, is displayed to the right. C1 represents the point of maximum counts and C2 represents counts at the time of 2 × T_{max}. The QP/QS ratio was 2.25 and the C2:C1 ratio was 0.66; both indicate a left-to-right shunt.

the peak of the time activity curve is proportional to blood volume, calculation of the areas under the initial lung peak (A_1) and the recirculation peak (A_2) provides an assessment of the magnitude of the shunt.[1a, 2, 5, 6] The pulmonary to systemic flow ratio, QP/QS, is calculated by the equation:

$$QP/QS = A_1/A_1 - A_2,$$

where A_1 = area under the first lung peak and A_2 = area under the second or recirculation peak.

Normal animals should have a pulmonary to systemic flow ratio of 1 to 1.2. A QP/QS greater than 1.2 indicates a left-to-right shunt.[5, 6]

An alternative method of analysis requires measurement of lung counts at specific time intervals during the peak and washout FPRA periods. First, the time interval from initial appearance of the bolus to the time of peak lung activity is recorded (T_{max}). Then, lung counts at the time of peak activity (C1) and at the time of 2 × T_{max} (C2) are determined. The ratio (C2 to C1) provides an estimate of shunt size.[1, 5] The normal C2 to C1 ratio is 0.30 to 0.50.[1, 5] Values above this range are seen with left-to-right shunts (Fig. 10–3).

RIGHT-TO-LEFT SHUNTS

Right-to-left shunts are characterized in FPRA studies by the simultaneous appearance of activity in the pulmonary artery and aorta (Fig. 10–4). Shunted radioactive blood appears early in the systemic circulation because it bypasses the pulmonary circulation. In patients with small shunts, the thoracic aorta may be obscured by the relatively high activity in the lungs. For this reason, it is important to include the abdominal aorta and right kidney in the field of view to view the early appearance of the radiopharmaceutical in these locations.

A simple and elegant way to diagnose and quantify a right-to-left shunt is by intravenous injection of ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA).[2] Because of its large particle size (10 to 90 microns), ^{99m}Tc-MAA is trapped in the capillaries. In normal animals, virtually all the ^{99m}Tc-MAA localizes in the lung in a pattern reflective of pulmonary blood flow. In animals with right-to-left shunts, some of the activity bypasses the lung and goes directly into the systemic circulation, resulting in excessive extrapulmonary activity (Fig. 10–5).[7] The percentage of shunted blood is calculated from the following formula:[2, 8]

$$\%Shunt = Extrapulmonary\ Activity / Extrapulmonary + Pulmonary\ Activity$$

EVALUATION OF VENTRICULAR FUNCTION

Ventricular function can be assessed by first-pass radionuclide angiocardiography (FPRA) or gated equilibrium radionuclide angiocardiography (ERNA).[1] First-pass studies have the advantage of displaying images of the right and left sides of the heart independently because the radiopharmaceutical agent passes through the cardiac chambers at different times.[1a, 9] This technique is particularly well suited for right ventricular evaluation, which is otherwise difficult to isolate. The disadvantage of FPRA is that only 4 to 6 cardiac cycles can be evaluated as the bolus quickly passes through the ventricles. In contrast, ERNA studies record data from several hundreds of cardiac cycles, thereby providing a more useful assessment of average cardiac function. Unfortunately, the accuracy of ERNA studies is limited in dogs and cats by unavoidable overlap of the left and right ventricles, so that the functional indices derived are not purely from an isolated ventricle.[10, 11] Nonetheless, gated ERNA is the preferred method of evaluating left ventricular function in humans[9, 12] and dogs.[10, 11, 13–18]

EQUILIBRIUM RADIONUCLIDE ANGIOCARDIOGRAPHY

Gated ERNA studies are obtained following intravenous injection of a blood pool agent, such as ^{99m}Tc-

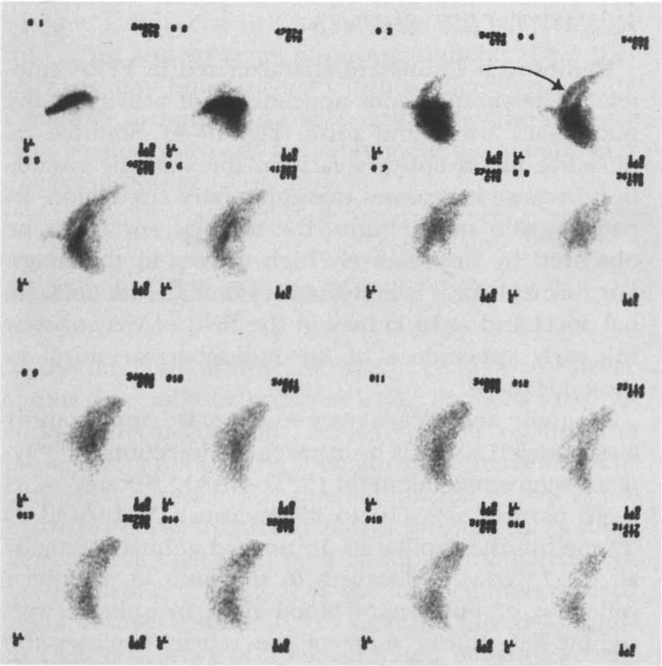


FIGURE 10–4

First-pass radionuclide angiocardiogram in an animal with tetralogy of Fallot. Note the simultaneous visualization of the aorta and main pulmonary artery during the dextrophase *(curved arrow)*, indicative of a right-to-left shunt.

labeled red blood cells (^{99m}Tc-RBC) or ^{99m}Tc-labeled human serum albumin (^{99m}Tc-HSA).[7] After equilibration with the blood pool, the activity in a given quantity of blood is directly related to its volume (Fig. 10–6). The computer synchronizes image acquisition with an electrical signal (the R wave) from the electrocardiogram so that a series of images representing various stages of the cardiac cycle may be obtained at specific time intervals.[19, 20] For adequate temporal resolution, at least 16 imaging frames per cardiac cycle are needed. In cats and small dogs, a pin-hole collimator is required to resolve the chambers of the heart adequately. Images from multiple sequential cardiac cycles are combined to form the final image set, which is temporarily and spatially smoothed and from which unwanted background activity is subtracted.[9, 21, 22] Because changes in activity in the ventricle during the cardiac cycle represent volume changes, a number of functional indices may be derived from the ventricular time activity (volume) curve, including ejection fraction, filling times, peak filling rates, and time and rate of ventricular ejection (Table 10–1).[9, 10, 20]

Ejection fraction (EF) is the most commonly used index of systolic function obtained from the radionuclide ventriculogram.[9, 12, 23] It is the percentage of the ventricular end-diastolic volume that is ejected during cardiac contraction and is determined from the maximum (end-diastolic) and minimum (end-systolic) ventricular counts. The EF is calculated using the following formula:

$$EF = \frac{\text{End-diastolic counts} - \text{end-systolic counts}}{\text{End-diastolic counts} - \text{background activity}} \times 100$$

Ejection fraction has been shown to be an important predictor of mortality in humans and dogs with congestive heart failure.[24–29] Although EF is the most widely reported index of ventricular systolic function, this index is influenced by changes in preload and afterload.[30] Gated ERNA studies of dogs with early, compensated mitral valvular insufficiency show an enlarged left atrium, increased end-diastolic volume, normal or small end-systolic left ventricular (LV) volume, and an increased ejection fraction (Fig. 10–7). After chronic volume overload, myocardial function de-

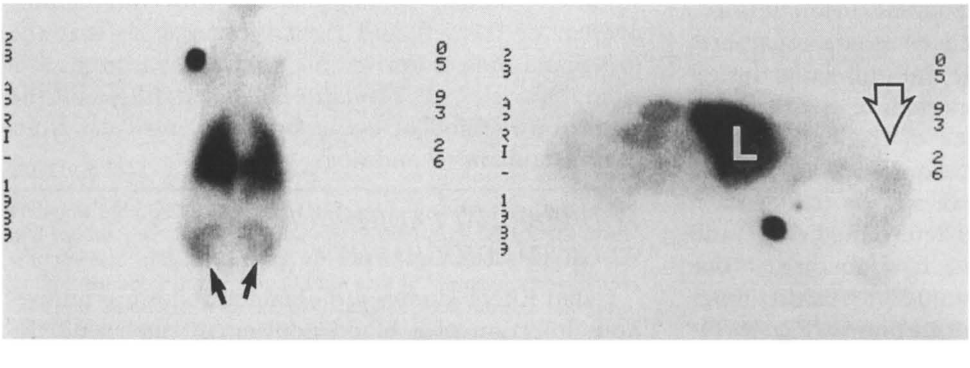


FIGURE 10–5

Dorsal and lateral images of an animal following injection of ^{99m}Tc-MAA. Note the pulmonary and extrapulmonary activity indicating the presence of a right-to-left shunt. The brain *(open arrow)* and kidneys *(small arrows)* have a large portion of the extrapulmonary activity. The focal accumulation in the left arm represents the injection site. L, pulmonary circulation.

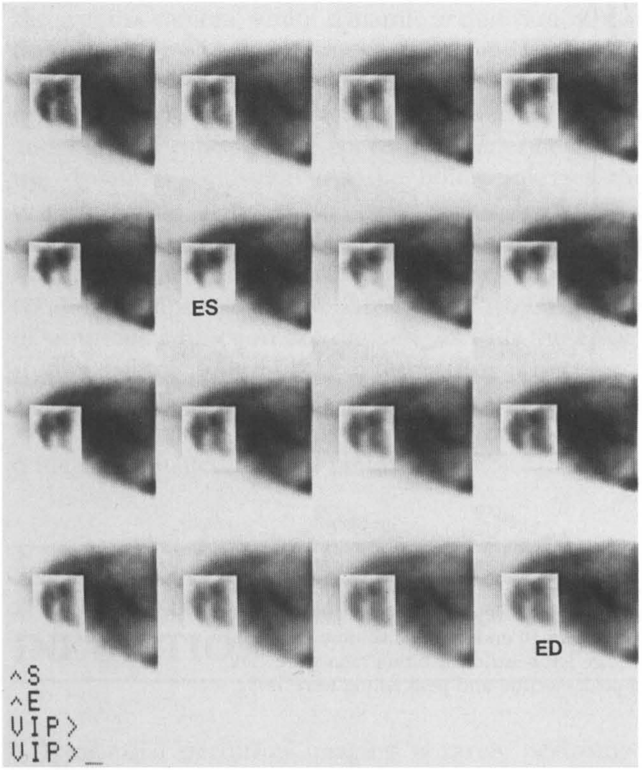


FIGURE 10–6

Multigated analysis of an equilibrium radionuclide ventriculogram from a normal dog. The images have been smoothed, and background activity is removed from the area of the heart *(square box)*. Note the separation of the left and right ventricles. A region of interest is fitted to each ventricle, and the activity therein is determined for each frame. Also note the change in size of the ventricles at end-systole *(ES)* and end-diastole *(ED)*.

clines, resulting in increased end-diastolic and end-systolic LV volumes, and a normal or reduced EF. Ejection of blood into the low-pressure left atrium invalidates the ejection fraction as a reliable indicator of myocardial function in dogs with mitral regurgitation. In this circumstance, end-systolic volume may be a more accurate indicator of myocardial function. Gated ERNA studies with dilated cardiomyopathy and doxorubicin-induced cardiac toxicity show LV dilation, diffuse wall motion abnormalities, and a diminished ejection fraction (Fig. 10–8). In such patients, EF provides a reliable measurement of the severity of myocardial dysfunction.

Gated ERNA studies are more sensitive than thoracic radiographs for staging the progression of cardiac disease, monitoring response to therapy, or offering a prognosis. Gated ERNA studies can be repeated several hours following a single injection of the radiopharmaceutical, allowing evaluation of the heart in a resting state and after exercise.[9, 13, 14, 17] Pharmaceutical challenge with dopamine has been used as an alternative to exercise.[13, 17, 18, 31] The ability of the heart to respond to such challenges provides a particularly sensitive index of cardiac dysfunction.[9, 17, 18] Regional wall motion may also be evaluated from ERNA studies by viewing the radionuclide ventriculogram in rapid sequence.

Other useful indices of ventricular function obtained by ERNA include the rates of ventricular ejection and filling (see Table 10–1). These indices are derived by obtaining the first derivative with respect to time of the ventricular volume curve. The rate of ventricular ejection reflects the ability of the myocardium to generate force. The ejection rate may be more sensitive than the ejection fraction for detecting inotropic changes in humans.[14, 26]

Gated ERNA offers a noninvasive means of measuring ventricular diastolic function (filling), which is altered in many cardiac diseases, especially those characterized by myocardial compliance failure such as myocardial ischemia, restrictive myocardial diseases, and hypertrophic cardiomyopathy. In many other diseases, diastolic dysfunction precedes or accompanies systolic dysfunction.[32–34] Fast heart rates and small cardiac volumes hamper the determination of ERNA diastolic indices in cats. Sinus arrhythmia also complicates the determination of diastolic function by traditional ERNA studies, causing spuriously low counts at the end of the volume curve. This can be minimized by rejecting data from heart beats outside a predefined R-R interval. When the heart rate is irregular, evaluation of diastolic filling on ERNA studies is facilitated by computers that acquire and store data in list mode. This method stores each scintillation count separately in a serial manner as opposed to traditional frame mode acquisition. It permits reconfiguration of cardiac images using forward and backward gating, facilitates frame alignment at the beginning and end of the cardiac cycle, and removes count drop-off resulting from sinus arrhythmia. Accurate assessment of diastolic function is improved.

Accurate assessment of RV function is difficult from

TABLE 10–1
Functional Indices Derived from Gated Equilibrium Radionuclide Studies in Normal Dogs

	Left Ventricle		Right Ventricle	
Parameter	*(Mean)*	*(SD)*	*(Mean)*	*(SD)*
Ejection fraction (%)	57	18	34	11
Emptying rate$_{max}$ (EDV/sec)	3.86	1.24	2.72	0.91
Emptying rate$_{avg}$ (EDV/sec)	3.04	0.99	2.02	0.67
Filling rate$_{max}$ (EDV/sec)	4.25	1.44	2.28	0.70
Filling rate$_{avg}$ (EDV/sec)	3.41	1.21	1.96	0.58
Time to peak emptying (msec)	122.72	12.91	123.49	19.87
Time to peak filling (msec)	90.07	8.09	91.85	11.44

EDV, end-diastolic volume.

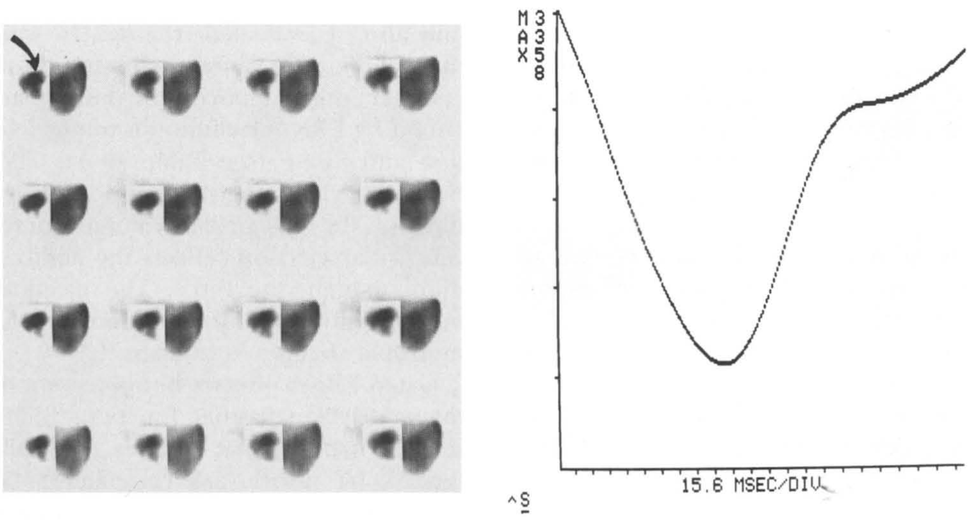


FIGURE 10–7

Multigated analysis of an equilibrium radionuclide ventriculogram from a dog with compensated mitral insufficiency. Note the large left atrium *(arrow)* on the image set on the left. The ventricular volume curve on the right shows the hyperkinetic left ventricle. The ejection fraction was 78% and the maximum and average left ventricular ejection rates were 6.10 end-diastolic volume (EDV)/sec and 5.32 EDV/sec, respectively. The maximum and average left ventricular filling rates were 7.42 EDV/sec and 6.22 EDV/sec, respectively. The times to peak ejection and peak filling were 78.32 msec and 63.42 msec, respectively.

equilibrium blood pool studies.[9, 35] The RV overlaps the LV, making it hard to isolate these chambers. Also, it is difficult to isolate the RV from the RA. Despite this limitation, a good correlation between right ventricular ERNA indices and hemodynamic measurements has been demonstrated in dogs, suggesting that these indices may be a useful noninvasive method of predicting changes in pulmonary artery pressure.[13]

FIRST-PASS RADIONUCLIDE ANGIOCARDIOGRAPHY

Left and right ventricular ejection fractions can be quickly obtained from FPRA studies. The volume of the injected dose must be small (0.5 ml) and injected rapidly to ensure delivery of a tight bolus of activity. The animal is positioned in lateral recumbency over

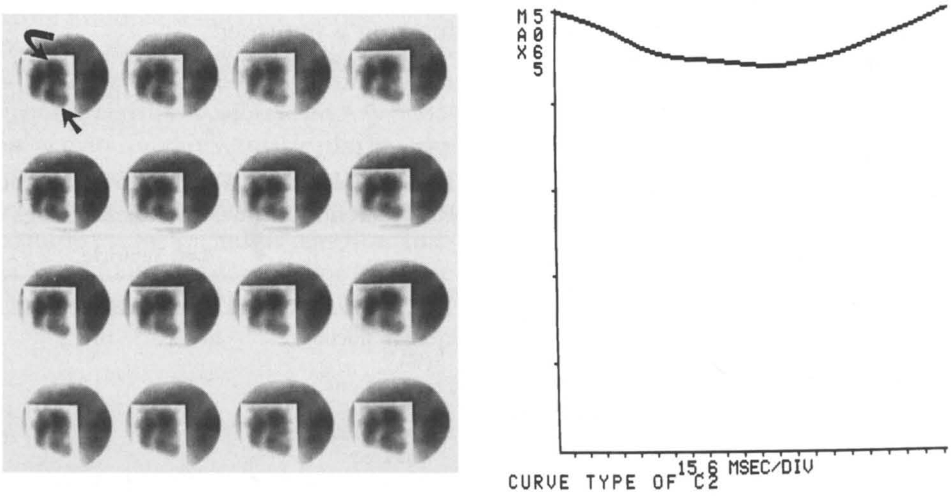


FIGURE 10–8

Multigated analysis of an equilibrium radionuclide ventriculogram from a dog with dilated cardiomyopathy. Note the large left ventricle *(straight arrow)* and atrium *(curved arrow)* on the image set on the left. The ventricular volume curve on the right shows very poor contractility. The ejection fraction was 17% and the maximum and average left ventricular ejection rates were 1.34 end-diastolic volume (EDV)/sec and 0.84 EDV/sec, respectively. The maximum and average left ventricular filling rates were 0.55 EDV/sec and 0.44 EDV/sec, respectively. The times to peak ejection and peak filling were 135.99 msec and 126.24 msec, respectively.

the gamma camera, and a dynamic acquisition, with a frame rate of 25 to 50 frames per second for 30 seconds, is initiated upon injection of the radiopharmaceutical. Regions of interest are drawn over the RV and LV, and time activity curves are generated from the dynamic acquisition. As the bolus traverses the ventricles, several peaks and valleys representing the diastolic and systolic phases of the cardiac cycle are identified. Three to six cardiac cycles are combined to create a composite volume curve from which indices of ventricular function are derived. As with the ERNA studies, subtraction of background activity is necessary. Right-sided heart function is commonly assessed by FPRA in humans, but this technique has not been critically evaluated in dogs or cats.

EVALUATION OF MYOCARDIAL PERFUSION, ISCHEMIA, AND INFARCTION

Myocardial perfusion imaging is rarely performed in veterinary medicine owing to the low incidence of atherosclerotic coronary artery disease. However, it might be relevant in canine subvalvular aortic stenosis and feline myocardial diseases, in which coronary artery lesions and myocardial fibrosis are common. A variety of radiopharmaceuticals are available to evaluate myocardial perfusion. Thallium-201 has gained widespread acceptance as a myocardial perfusion imaging agent.[7] The biologic properties of ^{201}TI are similar to those of potassium. Initial myocardial uptake of ^{201}TI is proportional to myocardial blood flow, and approximately 85 percent of the injected ^{201}TI is removed by the myocardium in a single pass. Within several hours, ^{201}TI redistributes in the heart to reflect the distribution of the potassium pool. Myocardial defects (cold spots) suggest the presence of a fixed abnormality, such as a permanent scar. Defects observed on the initial ^{201}TI scan but which demonstrate improved uptake on the delayed scan generally indicate myocardial ischemia. Cardiac perfusion images can be made with a conventional gamma camera, but a single photon emission computed tomography (SPECT) camera is preferred. Tomographic transaxial plane images allow circumferential evaluation of the ventricular wall, improving detection and localization of perfusion defects.

Two ^{99m}Tc-labeled agents, sestamibi and teboroxime, were recently introduced as alternatives to ^{201}TI.[36, 37] ^{99m}Tc has superior physical characteristics, resulting in improved image quality in comparison with ^{201}TI.[1] Like ^{201}TI, ^{99m}Tc-sestamibi and ^{99m}Tc-teboroxime are taken up by the myocardium in proportion to blood flow. Unlike ^{201}TI, ^{99m}Tc-sestamibi is not redistributed within the myocardium, and its peak extraction is less than that of ^{201}TI.[36–39] ^{99m}Tc-teboroxime is more efficiently extracted by the myocardium than the other agents, and it has a very rapid washout period.

COMPUTED TOMOGRAPHY OF THE HEART

Computed tomography (CT) is an x-ray technique that displays cross-section images of the body (Fig. 10–9). The usual imaging plane is perpendicular to the long axis of the body (transaxial plane) as the x-ray tube rotates around the patient during the exposure. The relative intensity of the x-ray beam, as it emerges from the patient, is recorded by an array of x-ray detectors. A computer is used to reconstruct a cross-section image from the detector data.[40, 41] The CT scanner acquires one image at a time then moves the patient to the next imaging plane. The thickness of each image slice is typically 2 to 10 mm. Because the animal must remain motionless during the entire scan, general anesthesia is required. Intravenous contrast infusion is necessary to identify vessels and the margins of the cardiac chambers.

The most relevant limitation of CT scanning is the relatively long acquisition time required for each image slice. Motion results in serious image degradation.[40] Cardiac imaging is not feasible in older scanners with long scan times (10 seconds or greater).[42] Even new scanners (third and fourth generation) with scan times of 1 to 5 seconds will have some motion artifact.

FIGURE 10–9

Contrast-enhanced computed tomograph of a 12-year-old dog. A large mass *(M)* is evident overlying the cranial heart base. It was surgically reduced and treated with radiation therapy. Histologic evaluation was chemodectoma. (Courtesy of Dr. Ann Hohenhaus.)

Crude cardiac studies may be accomplished using a CT scanner with 1- to 2-second scan times and dynamic scanning capability.[42] A dynamic scan is a series of sequential 1- to 2-second scans with little or no delay between images. Scans may be obtained without table (patient) advancement to produce a single-level dynamic study. Alternatively, dynamic scanning can be performed with table movement between scans to obtain a multilevel dynamic scan. Experimental canine studies showed good correlation of septal wall thickness measurements obtained from dynamic CT images with necropsy measurements.[43] Eliminating the problem of physiologic heart motion requires ECG-gated acquisitions or CT scanners capable of millisecond scan times.[42] Gating the acquisition to the patient's ECG provides stop action images of the heart, but this option is not available with most commercial CT scanners.[42, 44, 45] High-speed CT scanners capable of 50-msec scan times (Cine CT) have limited availability.[46, 47]

MAGNETIC RESONANCE IMAGING OF THE HEART

MRI is a safe and noninvasive imaging technique that does not require contrast media injection or ionizing radiation.[48] Images are created from radio frequency signals generated from the patient's hydrogen protons. The anesthetized patient is placed within a strong magnetic field and the hydrogen protons are intermittently excited by a radio frequency signal. A computer constructs an image based on the signals emitted when the hydrogen protons relax. Acquisition time varies with the sequence of radio frequency pulses and the number of the tomographic images.

MRI has excellent contrast resolution. The cardiac chambers and great vessels are easily visualized because rapidly flowing blood is void of signal (appearing black) on conventional T_1 spin-echo sequences.[49] As in CT imaging, physiologic cardiac motion must be compensated for by ECG gating. However, software for gating MRI acquisition is available on many new commercial scanners.[50, 51] Gated MRI studies define cardiac chamber morphology with the precision of angiocardiography and echocardiography.[52–54] Unlike CT scans, MRI can create cross-sectional images of the heart in any anatomic plane (Fig. 10–10), facilitating study interpretation and calculation of chamber volume, myocardial mass, and a variety of functional indices. The pericardium, cardiac tumors, and intracardiac thrombi may be more easily seen by MRI than by echocardiography. The ability of MRI to provide functional assessment of cardiac chambers and image blood flow makes it excellent for evaluating congenital and acquired heart diseases.[54–56]

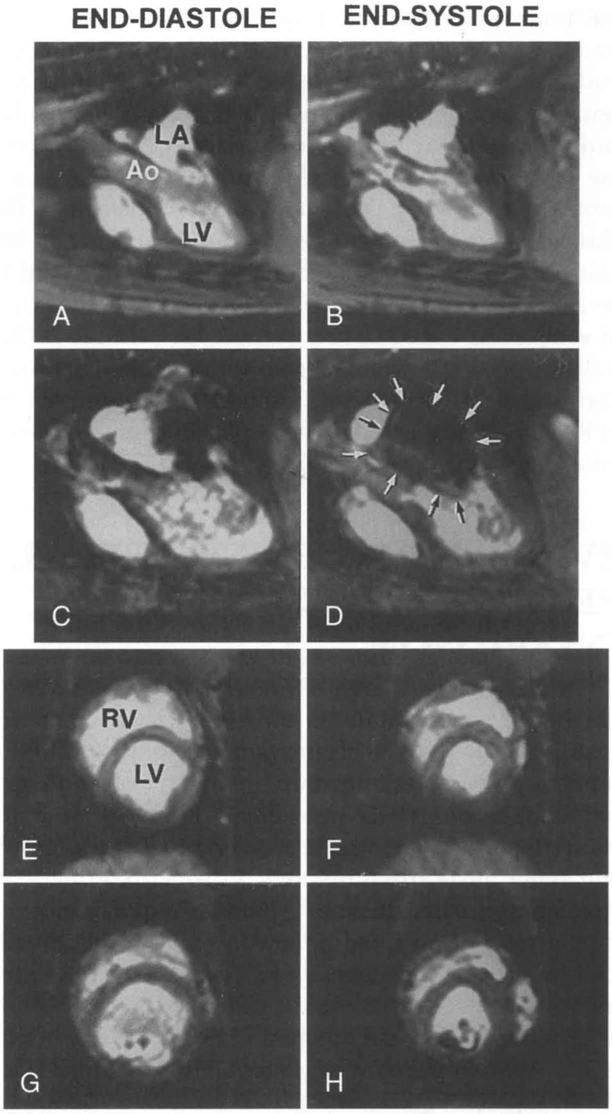


FIGURE 10–10

Magnetic resonance images depicting long axis (A–D) and short axis (E–H) views from a dog with experimental mitral regurgitation induced by cutting several chordae tendineae. A 1.5-T whole body imaging system (Philips Gyroscan, Shelton, CT) utilizing a gradient echo pulse sequence was used. Images were obtained for 16 to 20 phases of the cardiac cycle and averaged over the respiratory cycle during a 15-minute period. During the preoperative stage (A, B, E, F), the cardiac chambers are normal. Four months postoperative (C, D, G, H), there is substantial dilation of the left atrium (C, D) and left ventricle (C, D, G). Notice the severe mitral regurgitation outlined by arrows (D). Ao, ascending aorta; LA, left atrium; LV, left ventricle; RV, right ventricle. (Modified from Dell'Italia L, Meng QC, Balcelis E, et al. Increased ACE and chymase-like activity in cardiac tissue of dogs with chronic mitral regurgitation. Am J Physiol 269 [Heart Circ Physiol 38]: H2065–2073, 1995.)

New cardiac MRI applications include real-time acquisitions of cardiac structure (Cine MRI) and evaluation of myocardial perfusion using contrast agents.[57–60]

REFERENCES

1. Zaret BL, Wackers FJ. Nuclear cardiology. N Engl J Med 329:775, 1993

1a. Berger HJ, Zaret BL. Radionuclide assessment of cardiovascular performance. *In* Freeman LM (ed): Freeman and Johnson's Clinical Radionuclide Imaging. 3rd ed. Orlando, FL, Grune and Stratton, 1984, p 364

2. Kurug AR, Treves S. Pediatric cardiovascular nuclear medicine. *In* Gottschalk AG, Hoffer PB, Potchen EJ (eds): Diagnostic Nuclear Medicine. 2nd ed. Baltimore, Williams & Wilkins, 1988, p 414

3. Liebow AA, Hales MR, Bloomer WE, et al. Studies on the lung after ligation of the pulmonary artery: II. Anatomic changes. Am J Pathol 26:177, 1950

4. Thrall DE, Badertscher RR, Lewis RE, et al. Collateral pulmonary circulation in dogs experimentally infected with *Dirofilaria immitis:* Its angiographic evaluation. Vet Radiol 21:131, 1980

5. Allhands RV, Twardock AR, Boero MJ. Uptake of ^{99m}TcMDP in muscle associated with a peripheral nerve block. Vet Radiol Ultrasound 28:181, 1987

6. Brawner WR, Daniel GB. Nuclear imaging. Vet Clin North Am 23:379, 1993

7. McAfee JG, Subramanian G. Radioactive agents for imaging. *In* Freeman LM (ed): Freeman and Johnson's Clinical Radionuclide Imaging. 3rd ed. Orlando, FL, Grune & Stratton, 1984, p 55

8. Gates GF, Orme HW, Dore EK. Cardiac shunt assessment in children with macroaggregated albumin technetium-99m. Radiology 112:649, 1974

9. DePuey EG. Evaluation of cardiac function with radionuclides. *In* Gottschalk AG, Hoffer PB, Potchen EJ (eds): Diagnostic Nuclear Medicine. 2nd ed. Baltimore, Williams & Wilkins, 1988, p 355

10. Daniel GB, Tucker RL, Bright JM, et al. Utilization of instantaneous ejection volume images to produce ventricular volume curves from an equilibrium radionuclide ventriculogram. Vet Radiol Ultrasound 34:276, 1993

11. Sisson D, Daniel GB, Twardock AR. Comparison of left ventricular ejection fraction determined in normal anesthetized dogs by echocardiography and gated equilibrium ventriculography. Am J Vet Res 50:1840, 1989

12. Adams WE, Clausen M, Hellwig D, et al. Radionuclide ventriculography (equilibrium gated blood pool scanning)—its present clinical position and recent developments. Eur J Nucl Med 13:637, 1988

13. Arrington KA, Bright JM, Daniel GB. The use of gated radionuclide ventriculography as a noninvasive method of evaluating right ventricular function in dogs with experimentally induced congestive heart failure. Sci Proc ACVIM, 1993, p 930

14. Daniel GB, Arrington KA, Bright JM, et al. Evaluation of gated radionuclide ventriculography to assess right and left ventricular function in an experimental right heart failure model. Proceedings, ACVR, 1992

15. Sisson D. The clinical evaluation of cardiac function. *In* Ettinger S (ed): Textbook of Veterinary Internal Medicine. 3rd ed. Philadelphia, WB Saunders, 1989, p 923

16. Van-den-Brom WE, Stokhof AA. Radionuclide ventriculography in the normal dog. Equilibrium studies. Res Vet Sci 47:333, 1989

17. Ettinger SJ. Ordering diagnostic tests in cardiovascular disease. *In* Hamlin RL (ed): Efficacy of Cardiac Therapy. Philadelphia, WB Saunders, 1991, p 1081

18. Sisson D. The clinical evaluation of cardiac function. *In* Ettinger S (ed): Textbook of Veterinary Internal Medicine. 3rd ed. Philadelphia, WB Saunders, 1989, p 923

19. DePuey EG, Rozanski A. Pharmacological and other nonexercise alternatives to exercise testing to evaluate myocardial perfusion and left ventricular function with radionuclides. Semin Nucl Med 21:92, 1991

20. Movahed A, Reeves WC, Rose GC, et al. Dobutamine and improvement of regional and global left ventricular function in coronary artery disease. Am J Cardiol 66:375, 1990

21. Royal HD. Computer analysis of gated radionuclide ventriculograms: Practical considerations. *In* Williams AG, Eckel CG (eds): Practical Computer Applications in Radionuclide Imaging. New York, Churchill Livingstone, 1987, p 161

22. Fogelman I, Maisey M. An Atlas of Clinical Nuclear Medicine. St. Louis, CV Mosby, 1988

23. Berger HJ, Zaret BL. Radionuclide assessment of cardiovascular performance. *In* Freeman LM (ed): Freeman and Johnson's Clinical Radionuclide Imaging. 3rd ed. Orlando, FL, Grune & Stratton, 1984, p 364

24. Robinowitz A, Wexler JP, Blaufox MD. Quantification of the radionuclide image: Theoretical concepts and the role of the computer. *In* Freeman LM (ed): Freeman and Johnson's Clinical Radionuclide Imaging. 3rd ed. Orlando, FL, Grune and Stratton, 1984, p 261

25. Mangschau A, Karlsen RL, Lippestad CT, et al. Systolic time intervals and ejection fraction in assessing left ventricular performance following acute myocardial infarction.. A comparison of systolic time intervals and equilibrium radionuclide ventriculography. Acta Med Scand 215:341, 1984

26. Philips HR, Levine FH, Carter JE, et al. Mitral valve replacement for isolated mitral regurgitation: Analysis of clinical course and late postoperative left ventricular ejection fraction. Am J Cardiol 48:647, 1981

27. Bonow RO, Ostrow HG, Rosing DR, et al. Effects of verapamil on left ventricular systolic and diastolic function in patients with hypertrophic cardiomyopathy: Pressure-volume analysis with a nonimaging scintillation probe. Circulation 68:1062, 1983

28. Holman BL. Nuclear cardiology. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 3rd ed. Philadelphia, WB Saunders, 1988, p 311

29. Lazor L, Russell JC, DaSilvia J. Use of multiple uptake gated acquisition scans for preoperative assessment of cardiac risk. Surg Gynecol Obstet 167:234, 1988

30. Stokhof AA, Brom WE, Van-den-Brom WE. Survival time in dogs with spontaneous atrial fibrillation related to scintigraphically measured cardiac performance. Vet Q 12:161, 1990

31. Bough EW, Gandsman EJ, North DL, et al. Gated radionuclide angiography evaluation of valve regurgitation. Am J Cardiol 46:423, 1980

32. Rankin LS, Moos S, Grossman W. Alternations in preload and ejection phase indices of the left ventricular performance. Circulation 51:910, 1975

33. Pierard LA, DeLandsheere CM, Berthe C, et al. Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: Comparison with positron emission tomography. J Am Coll Cardiol 15:1021, 1990

34. Bonow RO, Ostrow HG, Rosing DR, et al. Effects of verapamil on left ventricular systolic and diastolic function in patients with hypertrophic cardiomyopathy: Pressure-volume analysis with a nonimaging scintillation probe. Circulation 68:1062, 1983

35. Bonow RO. Radionuclide angiographic evaluation of left ventricular diastolic function. Circulation 84:208, 1991
36. Spirit P, Maron BJ, Bonow RO. Noninvasive assessment of left ventricular diastolic function: Comparative analysis of Doppler echocardiographic and radionuclide angiographic techniques. J Am Coll Cardiol 7:518, 1986
37. Ratner SJ, Huang PJ, Friedman MI, et al. Assessment of right ventricular anatomy and function by quantitative radionuclide ventriculography. J Am Coll Cardiol 13:354, 1989
38. Leppo JA, DePuey EG, Johnson LL. A review of cardiac imaging with sestamibi and teboroxime. J Nucl Med 32:2012, 1991
39. Beller GA, Watson DD. Physiological basis of myocardial perfusion imaging with the technetium 99m agents. Semin Nucl Med 21:173, 1991
40. Gibbons RJ. Technetium 99m sestamibi in the assessment of acute myocardial infarction. Semin Nucl Med 21:213, 1991
41. Berman DS, Kiat H, Van-Train K, et al. Technetium 99m sestamibi in the assessment of chronic coronary artery disease. Semin Nucl Med 21:190, 1991
42. Miraldi F, Wiesen EJ. Imaging principles in computed tomography. *In* Haaga JR, Alfidi RJ (eds): Computed Tomography of the Whole Body. 2nd ed. St. Louis, CV Mosby, 1988, p 1
43. Moore SC, Judy PF. Cardiac computed tomography using redundant-ray prospective gating. Med Phys 14:193, 1987
44. Hathcock JT, Stickle R. Principles and concepts of computed tomography. Vet Clin North Am 21:399, 1993
45. Johnson RA, Rubin LJ. Noninvasive evaluation of right ventricular function. Clin Chest Med 8:65, 1987
46. Churchill RJ. CT of the heart. *In* Haaga JR, Alfidi RJ (eds): Computed Tomography of the Whole Body. 2nd ed. St. Louis, CV Mosby, 1988, p 649
47. Oyama Y, Uji T, Hirayama T, et al. Gated cardiac imaging using a continuously rotating CT scanner: Clinical evaluation of 91 patients. Am J Radiol 142:865, 1984
48. Lipton MJ, Higgins CB, Farmer D, et al. Cardiac imaging with high-speed Cine-CT scanner: Preliminary results. Radiology 152:579, 1993
49. Skioldebrand CG. The functional and anatomic evaluation of the cardiovascular system with rapid-acquisition computed tomography. Circulation 61:960, 1980
50. Widmer WR, Buckwalter KA, Braunstein EM, et al. Principles of magnetic resonance imaging and application to the stifle joint in dogs. J Am Vet Med Assoc 198:1914, 1991
51. Bradley WG, Waluch V, Lai KS, et al. The appearance of rapidly flowing blood on magnetic resonance imaging. Am J Radiol 143:1167, 1984
52. Pettigrew RI. Cardiovascular imaging techniques. *In* Stark DD, Bradley WG (eds): Magnetic Resonance Imaging. 2nd ed. St Louis, Mosby Year Book, 1992, p 1605
53. Erlichman M. Surface/specialty coil devices and gating techniques in magnetic resonance imaging. Health Technol Assess Rep, 1990, p 1
54. Kondo C, Higgins CB. Congenital heart disease. *In* Stark DD, Bradley WG (eds): Magnetic Resonance Imaging. 2nd ed. St Louis, Mosby Year Book, 1992, p 1531
55. Mogelvang J, Stokholm KH, Saunamaki K, et al. Assessment of left ventricular volumes by magnetic resonance in comparison with radionuclide angiography, contrast angiography and echocardiography. Eur Heart J 13:1677, 1992
56. Allison JD, Flickinger FW, Wright JC, et al. Measurement of left ventricular mass in hypertrophic cardiomyopathy using MRI: Comparison with echocardiography. Magn Reson Imaging 11:329, 1993
57. Akagi T, Kato H, Kiyomatsu Y, et al. Evaluation of atrial, ventricular and atrioventricular septal defects by cine magnetic resonance imaging. Acta Paediatr Jpn 34:295, 1992
58. Wiles HB, Henrich D, Haase A, et al. Imaging congenital heart disease. Pediatr Clin North Am Magn Reson Imaging 8:377, 1990
59. Hardy CJ, Darrow RD, Nieters EJ, et al. Real-time acquisition, display, and interactive graphic control of NMR cardiac profiles and images. Magn Reson Med 29:667, 1993
60. Zerhouni EA. New directions in cardiac magnetic resonance imaging. Top Magn Reson Imaging 2:67, 1990

IV

Abnormal Cardiovascular Function and Principles of Therapy

11

Pathophysiology of the Failing Heart

ROBERT L. HAMLIN

DEFINITIONS OF HEART FAILURE

Heart failure or congestive heart failure is a clinical syndrome—not a disease. It results from a pathophysiologic interaction among the heart and neuroendocrine and vascular systems. When the heart cannot deliver blood to meet tissue metabolic needs, or does so at elevated filling pressures, impaired organ function, reduced quality and duration of life, and death may result.[1,2]

Heart failure refers to a heart that pumps an inadequate volume of blood or the blood which is pumped is maldistributed, resulting in inadequate tissue oxygen delivery. Tacit in this definition is adequate venous cardiac return, which differentiates heart failure from shock.[3]

Congestive heart failure (CHF) describes impaired cardiac function, which results in elevated venous and capillary pressures. This causes organs to become congested with blood or laden with edema fluid.

Failing heart is a third entity described in terms of how the myocardium functions. It is different from both heart failure or CHF, which are clinical entities. A patient may have a failing heart and may not be in heart failure. However, CHF is almost always associated with a failing heart.

Heart failure and CHF manifest clinical signs that can be observed during physical examination or conveyed by a pet owner. In contrast, a failing heart is described only in terms of physiology, requiring laboratory measurements of specific functional parameters.

THE FAILING HEART

The failing heart may be defined by different parameters. These include (1) *biochemical,* in which the rate of energy release by ATP (adenosine triphosphate) hydrolysis is reduced[4–11] (Fig. 11–1*A*); (2) *mechanical,* in which there is a reduced maximal velocity of myocardial fiber shortening achieved at zero loading conditions[12–17] (Fig. 11–1*B*); and (3) *functional,* in which there is a lower than expected force of contraction, considering the volume of blood (preload) in the chamber just before it contracts[18–23] (Fig. 11–1*C*). The property of the heart to contract once stimulated is termed *myocardial contractility,* or the *inotropic state.*[21] Thus, the failing heart has reduced myocardial contractility and is in a negative inotropic state.[12]

BIOCHEMICAL DERANGEMENTS

Muscle contraction results from the shortening of sarcomeres and is seen microscopically as reduction in the Z-Z interval.[24] This shortening results

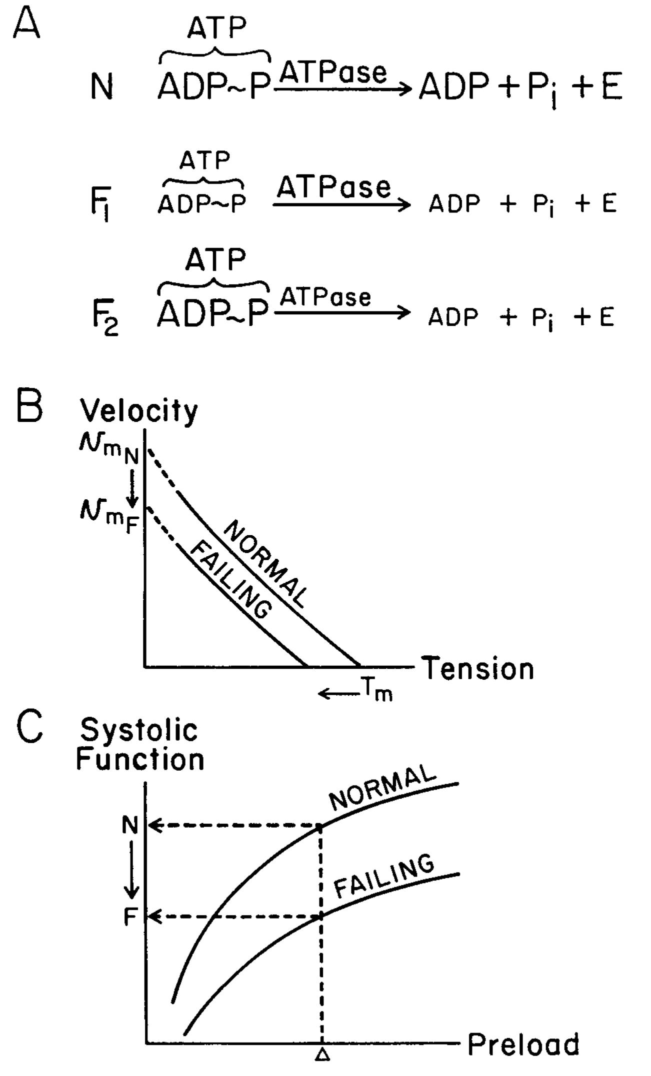


FIGURE 11–1

Methods for describing the failing heart. (A) Equations illustrating relative states of myocardial energy production. The ATP molecule is actually a molecule of ADP to which a final phosphorus atom is held by a high-energy bond. If this bond is broken, energy is released, which serves as the fuel for both myocardial contraction and relaxation. *N* depicts the normal state. F_1 shows reduced energy production because of decreased ATP substrate, although ATPase concentration is normal. F_2 shows reduced energy production associated with decreased amounts of ATPase, although ATP concentration is normal. (B) Graph contrasting the failing and normal myocardium at conditions of zero loading. The failing heart generates a reduced maximal velocity (V_m) of fiber shortening at any level of tension compared with the normal heart. The maximal tension (T_m) generated may also be reduced in the failing heart, but depends on the state of myocardial contractility plus the degree of fiber stretch (i.e., preload) just before contraction begins. (C) A failing ventricle can be expressed by Frank-Starling curves as illustrated here. In the failing heart they show that for any given preload (end-diastolic volume), the force of contraction generated (systolic function) is less than anticipated compared with the normal heart.

from heavy meromyosin cross-bridges swinging (cycling) and tugging on the actin filaments to which the Z bands are attached (see Fig. 3–6). All the energy for this motion—and for relaxation as well—arises from the hydrolysis of ATP into ADP (adenosine diphosphate) (Fig. 11–1*A*) and inorganic phosphate (Pi). The energy for contraction and relaxation is what holds the Pi to the ADP molecule to form ATP.[5] If ATP or ATPase is lacking, insufficient energy may be available for both contraction and relaxation.[22]

MECHANICAL DERANGEMENTS

The failing heart can be expressed using the velocity-tension curve (Fig. 11–1*B*) developed from studying a strip of myocardium.[15, 20] If the strip is stimulated and not permitted to contract because of a large mass hanging on it, the strip will generate a certain tension (maximal tension, T_m). That tension will depend upon both the inotropic state (i.e., the velocity with which the heavy meromyosin cross-bridges cycle) and how stretched the muscle is just before it is stimulated. As the mass suspended from the muscle becomes lighter and lighter (i.e., the muscle must lift, or try to lift, a lighter and lighter mass), the contracting muscle will generate less tension, and the velocity of shortening will become greater and greater. In fact, the relationship between shortening velocity (plotted on the ordinate) versus the tension developed (plotted on the abscissa) forms half of a hyperbola.

It is impossible to determine the velocity of shortening against zero load (i.e., against no resistance). Even if all mass is removed from the muscle strip, it must still shorten against its own mass. To determine the maximal velocity of shortening that may occur only under conditions of no load, the curve must be extrapolated to conditions of zero loading. The Y-axis intercept, occurring at the point where no tension is developed, will be the maximal velocity of fiber shortening (v_m). This cannot be influenced by loading conditions since the muscle strip is unloaded. Rather, it is determined by the velocity with which the heavy meromyosin heads cycle, and this velocity is a measure of the inotropic state.

In a muscle strip removed from the *failing heart,* both maximal velocity of fiber shortening (v_m) and maximal tension (T_m) of the velocity-tension curve are reduced because the rate of cycling of each heavy meromyosin head slows; if the muscle has not been stretched further to engage more heavy meromyosin heads, there are no more heads to cycle and to generate more tension. If each head cycles more slowly, as in a negative inotropic state, but the fibers are stretched to engage more heads and to add more Ca^{++} to the excitation-contraction process, T_m may not only be normal but could be greater than normal, even though v_m is reduced. That is why v_m rather than T_m is the measure of myocardial contractility, which is reduced in a failing heart.

FUNCTIONAL DERANGEMENTS

Finally, the failing heart can be expressed using Frank-Starling curves (see Fig. 3–7). These relate systolic function on the ordinate to ventricular end-diastolic blood volume (i.e., the preload) on the abscissa (Fig. 11–1*C*). For any increase in preload, the measures of systolic function—the pressure developed, stroke volume, cardiac output, maximal rate of rise of intraventricular pressure—will increase, not because the rate of cycling of heavy meromyosin heads increases, but because there are more heavy meromyosin heads to cycle. In fact, the greater the preload, the more heavy meromyosin heads that cycle. In a failing heart, the level of systolic function for a given preload is less than expected for a normal heart; for a given increase in end-diastolic volume (preload), the anticipated increment in stroke volume or maximal rate of rise of intraventricular pressure is reduced.

HYPERTROPHY, VOLUME OVERLOAD, AND GENESIS OF CONGESTIVE HEART FAILURE

In acquired cardiac disorders of the dog and cat, the left ventricle usually fails more frequently than the right ventricle, resulting in pulmonary congestion and edema. Occasionally right ventricular failure occurs, resulting in congestion of the liver and other systemic organs.

Normally the left atrial pressure (LAP) is approximately 5 mmHg and is responsible for filling the left ventricle (LV) to a normal end-diastolic volume (EDV) (Table 11–1). The EDV represents the cardiac preload (PL), which sets the number of heavy meromyosin cross-bridges for the subsequent contraction.

The following example can illustrate relationships between these parameters and the failing heart. For the sake of simplicity, assume that the LV free-wall thickness (WT) is 1 cm. A normally contracting LV with an EDV of 100 ml will (1) generate a pressure of about 100 mmHg (P) just before the aortic valve opens; (2) eject a forward stroke volume (SV) of approximately 60 ml of blood into the aorta during systole; and (3) leave behind approximately 40 ml as the end-systolic volume (ESV).

LAW OF LAPLACE

This relationship approximates the peak left ventricular wall tension, a measure of afterload. In its simplest version:

$$T = \text{Pressure} \times r/h,$$

where the average circumferential wall stress or tension (T) is directly related to the product of intraventricular pressure (Pressure) and internal cardiac chamber radius (r), and is inversely related to wall thickness (h). In illustrating this Laplace relationship in the following

TABLE 11–1
Hemodynamic Profiles of Myocardial Compensation and Cardiac Disease

	LAP (mmHg)	EDV (PL) (ml)	WT (cm)	SV (ml)	ESV (ml)	P (mmHg)	T (Units)
A. Normal	5	100	1.0	60	40	100	10,000
		(Dilated Cardiomyopathy)					
B. Failure	5	100	1.0	40	60	80	8,000
C. Dilated	15	120	0.8	60	60	100	15,000
D. Eccentric hypertrophy	15	120	1.2	60	60	100	10,000
E. Normal	5	100	1.0	60	40	100	10,000
		(Aortic Stenosis)					
F. Stenosis	5	100	1.0	40	60	200	20,000
G. Comp.	15	120	0.8	60	60	300	40,000
H. Concentric hypertrophy	15	120	3.6	60	60	300	10,000

LAP, left atrial pressure; EDV (PL), left ventricular end-diastolic volume (preload); WT, left ventricular wall thickness; SV, stroke volume; P, left ventricular pressure at the instant the aortic valve opens; T, peak myocardial tension (EDV × P/WT), also afterload.

A, E Normal heart: Left atrial pressure (LAP) is responsible for generating a particular left ventricular end-diastolic volume (EDV) or preload (PL). The end-systolic volume (ESV) is the volume of blood remaining within the left ventricle after the ventricle ejects its stroke volume (SV) [ESV = EDV − SV]. The pressure developed by the left ventricle just before the aortic valve opens (P) is also equal to the diastolic systemic arterial blood pressure. The peak myocardial tension (T) is approximated according to the law of Laplace, as the product of PL × P divided by WT.

B–D Progressive volume overload and myocardial failure due to dilated cardiomyopathy (see text for details): volume load of the left ventricle, shown as an increase in EDV, results from dilated cardiomyopathy. This results in eccentric hypertrophy characterized by a grossly enlarged left ventricular lumen and only a modestly enlarged left ventricular wall thickness.

F–H Left ventricular pressure overload from aortic stenosis results in a great increase in LV wall thickness with little change in ventricular luminal dimension, known as concentric hypertrophy. Notice that the peak tension (T) for pressure overload that initiates concentric hypertropy is much greater than for the peak tension in volume overload that initiates eccentric hypertrophy.

example, rather than using LV radius we will use preload or end-diastolic volume, which is curvilinearly related to radius (r) by the equation

$$EDV = 4/3 \text{ Pi } r^3.$$

In this example, assume that afterload for a normal LV is (100 ml × 100 mmHg)/1 cm, or 10,000 units. If the LV suddenly becomes cardiomyopathic (as from an acute infection with *Trypanosoma cruzi* in a dog or from taurine deficiency in a cat) and begins to fail, stroke volume decreases to 40 ml and the LV pressure (P) falls to 80 mmHg. Because of the reduced SV, the ESV increases to 60 ml (the weakened LV leaves more blood behind), and the afterload decreases to only 8000 units (Table 11–1*B*). Because stroke volume decreases and end-diastolic volume increases, blood dams up within the LA, and left atrial pressure increases to 15 mmHg. This increased LA pressure slightly overfills the left ventricle to an end-diastolic volume of 120 ml, 20 ml more than when the left atrial pressure was only 5 mmHg. Because end-diastolic volume is increased, LV wall thickness decreases. Despite the failing left ventricle, stroke volume returns to a normal 60 ml, and LV pressure (P) returns to a normal 100 mmHg (Table 11–1*C*) because of the Frank-Starling mechanism, which states that force of contraction increases when preload increases. The resulting reduced myocardial contractility (i.e., reduced rate of cycling of heavy meromyosin heads) and increased preload (i.e., the number of heavy meromyosin heads cycling) allows the diseased left ventricle to eject a normal stroke volume and, therefore, sustain a normal cardiac output. However, afterload increases to 15,000 units ([120 ml × 100 mmHg]/0.8 cm), end-systolic volume remains elevated to 120 ml, and left atrial pressure remains elevated to 15 mmHg. This compensatory mechanism permits cardiac output to remain normal, although at the expense of increased afterload and left atrial pressure. The consequences of these changes are discussed next.

MECHANISMS OF HYPERTROPHY

The major determinants of myocardial oxygen consumption are afterload, heart rate, and myocardial contractility.[25, 26]

ECCENTRIC HYPERTROPHY

When afterload increases, so does myocardial oxygen consumption. If oxygen consumption outstrips oxygen delivery, the myocardium may suffer oxygen debt.[27] Such oxygen debt activates adenylate cyclase, which augments the conversion of ATP to cyclic AMP (cAMP). Increased cAMP activates protein kinase (PK), which increases protein synthesis, resulting in hypertrophy (increased muscle mass). This hypertrophy is termed "eccentric hypertrophy" because the ventricular lumen is dilated and the free wall is either normal or slightly thicker than normal (Table 11–1*D*). Eccentric hypertrophy is caused by left ventricular *volume overload,* which is represented as an increase in end-diastolic volume. Thus, the LV free wall may become 1.2 cm thick, and the effect on afterload may be predicted by the law of Laplace (the afterload will become 120 ml × 100 mmHg, all divided by 1.2 cm, or will return to 10,000 units). This will re-establish a balance between oxygen demand and delivery and potentially prevent the consequences of sustained oxygen debt.[20–22]

CONCENTRIC HYPERTROPHY

Physiologic response to *pressure overload* such as aortic stenosis may be examined in a similar manner. Assume that the normal pressures, volumes, and tension are as stated earlier (Table 11–1*A*, *E*). After the "magical instant" that aortic stenosis is produced, left atrial pressure, LV end-diastolic volume, and LV wall thickness remain constant; stroke volume decreases due to interference to left ventricular ejection caused by the fixed outflow obstruction (i.e., aortic stenosis). Left ventricular pressure increases profoundly to 200 mmHg because the ventricle must eject against that increased interference (imagine how much more pressure you could generate pushing your hand against a 300-pound steel ball compared with pushing against a feather!). Myocardial tension increases dramatically to 20,000 units. Blood in the LV does not completely eject, and left atrial pressure increases to 15 mmHg because of this decrease in forward stroke volume (Table 11–1*F*). During the next instant, when LV end-diastolic pressure increases to 120 ml and the force of contraction increases because of the Frank-Starling effect, stroke volume returns to normal, LV pressure (P) increases even more to 300 mmHg, and peak LV pressure at the instant the aortic valve opens increases to 40,000 (Table 11–1*G*). This dramatic increase in tension initiates the steps leading to hypertrophy (Table 11–1*H*). Thus, LV wall thickness markedly increases to 3.6 cm, and myocardial tension actually falls to the normal 10,000, even though LV systolic pressure remains elevated. This dramatic hypertrophy, in which the LVFW becomes extremely thickened due to the enormous T, is *concentric hypertrophy,* a consequence of ventricular *pressure overload.*

With added myocardial mass, there may be a greater distance for diffusion of oxygen from capillary to mitochondria, as well as a relative decrease in mitochondrial numbers. Therefore, oxygen deprivation, myocyte death, and fibrosis may result.[28–31]

PATHOPHYSIOLOGIC RESPONSE TO VOLUME OVERLOAD

Meerson and associate list three stages that describe the ventricular response to volume overload.[32, 33] These include (1) myocardial damage, (2) hyperfunction, and (3) exhaustion.

MYOCARDIAL INJURY

During this initial stage, clinical signs result from heart failure that is associated with low cardiac output (see later) or venous and capillary distention. The ventricle dilates; myocardial fibers swell and separate; stores of high-energy phosphate and glycogen become depleted; lactate production increases; and mitochondrial mass, RNA levels, and protein synthesis increase. These responses appear to represent the consequences of oxygen debt and include a shift toward anaerobic energy production and increased muscle mass.

HYPERFUNCTION

During this second stage, which usually lasts for a relatively long time, clinical signs abate. Hypertrophy results from increased myocardial fiber diameter. The ratio of fiber mass to myocardial mass increases. There is a return toward normal with respect to glycogen and high-energy phosphate supplies, RNA levels, and protein synthesis.

MYOCARDIAL EXHAUSTION

In this final stage, clinical signs progressively increase. Both ventricular systolic and diastolic function deteriorate; the heart failure state worsens; and death becomes imminent. As the ratio of myocardial mass to capillary density increases, oxygen must diffuse a greater distance from capillaries to myocardial cells. Energy deprivation, myocardial degeneration, and replacement of myocardium by fibrous connective tissue result. The latter decreases myocardial contractile units and acts to stiffen the myocardium. It is thought that increased levels of angiotensin II may be responsible for augmented growth, as well as for the production of oxygen-free radicals that result in lipid peroxidation of cell membranes. Protein synthesis cannot replace the loss of contractile myocardium.

ADDITIONAL MYOCARDIAL CHANGES WITH HEART FAILURE

Some of the newly synthesized proteins contain fetal protein forms that tend to increase their rate of production.[34–36] There appears to be increased concentration of inhibitory G (G_i) protein.[37] This mediates the inhibition of adenylate cyclase, which decreases intracellular cyclic AMP and associated myocyte calcium influx, thereby reducing contractility. In addition, human studies of long-standing heart failure have reported hypothyroidism.[38] This may be due to a decreased rate of peripheral T_4 (thyroxine) to T_3 (triiodothyronine) conversion, as well as to reduced rates of T_4 production by the thyroid gland.

VOLUME OVERLOAD WITH PATENT DUCTUS ARTERIOSUS

The previous discussion has explained why the right or left ventricle enlarges and fails with valvular stenosis or insufficiency. However, why does the left ventricle fail with a patent ductus arteriosus (PDA)?

Figure 11–2 schematically compares the normal circulation with the circulation in PDA. Each ventricle normally pumps the same volume of blood during each cardiac cycle, and thus the pulmonary and systemic circulations carry the same volume of blood. Normally, the left ventricle pumps blood through the systemic circulation to the right atrium, and the right ventricle pumps blood through the lungs to the left atrium. Because of cardiac septation, no blood shunts left to right, even though pressures in the left cardiac chambers are higher than pressures in the corresponding right-sided heart chambers. In contrast, the circulation is disrupted with PDA due to communication between the aorta (in which the pressure varies between 120 and 80 mmHg) and the pulmonary trunk (in which pressure varies between 20 and 10 mmHg). Because of this patent ductal communication between aorta and pulmonary artery, and because the aortic pressure is always higher than pulmonary pressure, a quantity of blood (i.e., 200 ml per cardiac cycle) shunts through the PDA from aorta to pulmonary trunk. The resulting volume overload initiates eccentric hypertrophy of both left atrium and left ventricle, and the overstretching of the left ventricle initiates a cascade of structural changes (e.g., fibrosis, slippage of sarcomeres) and biochemical alterations (e.g., depletion of stores of high-energy phosphate) that ultimately precipitates left-sided heart failure.

Myocardial hypoxia or chronic stretch or both lead to important changes in myocardial diastolic function.[19, 39–41] An early effect of energy depletion is decreased myocardial compliance (lusitrope). This results in a reduced rate of ventricular relaxation, which

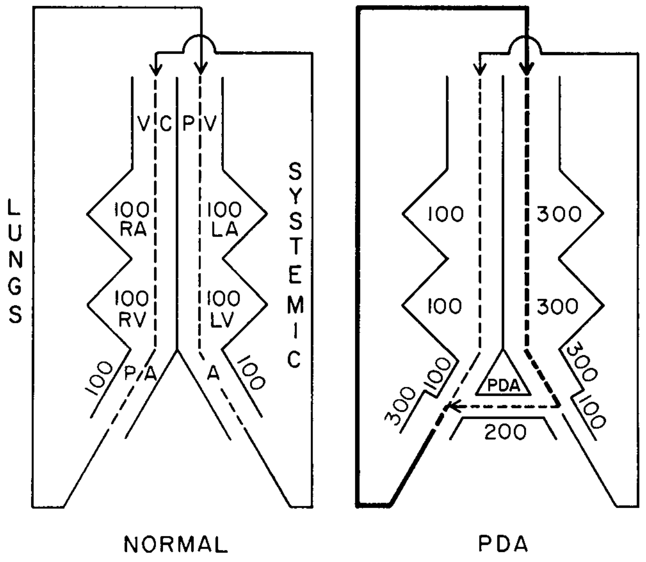


FIGURE 11-2

Diagrams of the normal pulmonary and systemic circulations and of an animal with patent ductus arteriosus (PDA). With PDA, a communication between the aorta and pulmonary trunk persists postnatally. Vessels are labeled VC (vena cava), PV (pulmonary vein), RA (right atrium), LA (left atrium), RV (right ventricle), LV (left ventricle), PA (pulmonary artery), and A (aorta). Nominal volumes of blood traversing or being pumped by each chamber or vessel are included for illustration. Therefore, for the *normal* circulation, both atria, both ventricles, and both pulmonary and systemic circulation carry or pump 100 units. In contrast with the PDA circulation, 200 units of blood shunts through the patent ductus from aorta to pulmonary artery. Thus, the PA, lungs, PV, LA, LV, and ascending aorta all carry three times the normal volume of blood. This results in engorgement and, in the case of LA and LV, eccentric hypertrophy. Of the 300 ml of blood which enters the ascending aorta, 200 ml shunt through the PDA. Therefore, normal amounts of blood are carried in the remainder of the aorta distal to the PDA, the systemic circulation, vena cava, RA, and RV, and the RA and RV are not hypertrophied. The reason the lungs can carry three times the normal amount of blood without developing higher pressure (i.e., pulmonary hypertension) is that the pulmonary circuit can both dilate existing vessels and recruit new vessels.

requires elevated ventricular filling pressure (i.e., left atrial and pulmonary venous and capillary pressures) in order to achieve satisfactory left ventricular filling. In addition, inadequate myocardial energy may have a negative inotropic effect. These changes either precipitate or aggravate the sequence of events leading to congestive heart failure. Altered diastolic function usually precedes altered systolic function.

GENESIS OF PULMONARY EDEMA

Increased left atrial pressure is a compensatory response to the failing left ventricle. It initiates a cascade of events that contributes to or causes clinical signs of congestive heart failure. If blood flows from pulmonary capillaries to the left atrium when left atrial pressure increases, then pulmonary capillary and pulmonary venous pressures also become elevated[42] (Fig. 11-3). This causes vascular engorgement with blood known as *congestion,* which adds mass to the lung and makes it stiffer. Increased lung weight and stiffness make inspiratory lung expansion more difficult. This may lead to fatigue of muscles of ventilation—in particular, the diaphragm—with possible exhaustion of those muscles and resultant asphyxia. Dilatation of pulmonary veins also leads to a bronchoconstrictive reflex that results in so-called "cardiac asthma" described in humans.[43, 44] Wet, heavy lungs also result in ventilation-perfusion inequalities, which lead further to asphyxia.

If pulmonary capillary engorgement becomes even more severe, such that the pulmonary capillary pressure reaches 18 to 22 mmHg (normal is < 12 mmHg), the rate that serum weeps from the pulmonary capillaries into the pulmonary lymphatics may exceed the rate that those lymphatics drain the pulmonary interstices, and fluid accumulates within the lung as pulmonary edema. Initially, this occurs around the smaller airways and blood vessels and leads to partial obstruc-

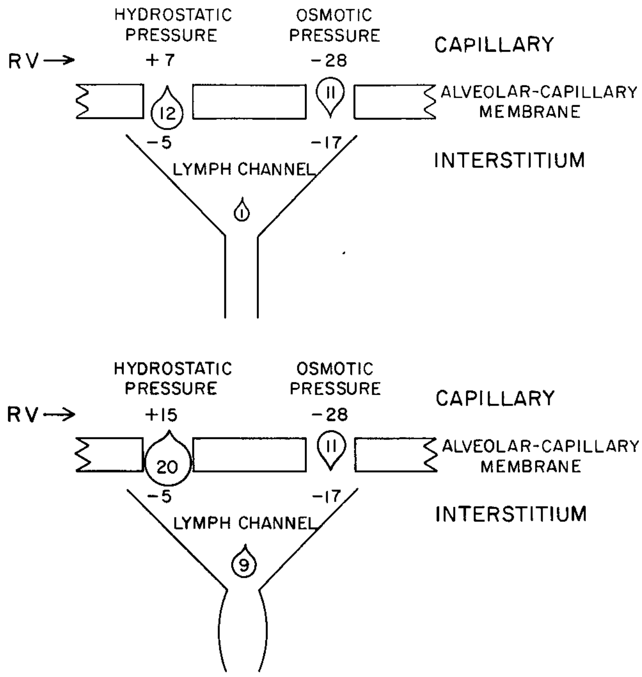


FIGURE 11-3

Diagrams of the circulation through pulmonary capillaries for the normal *(top)* and for the failing *(bottom)* left ventricle. The alveolar-capillary membrane separates the intracapillary space from the interstitial space. Values for either hydrostatic or osmotic (oncotic) pressures (mmHg) are labeled such that a plus sign (+) indicates a force pushing fluid out of the compartment, and a negative (−) sign indicates a force sucking fluid into the compartment. A teardrop containing a number represents the direction fluid would move—either into or out of the capillary. With inadequate left ventricular function *(bottom)*, capillary hydrostatic pressure (and lymph flow) increases. Lymphatic drainage is ultimately overwhelmed, and serum oozes into the interstitium faster than the pulmonary lymphatics can return the fluid to the capillaries. This fluid builds in the pulmonary interstitium as pulmonary edema.

tion of those airways and vessels (chapter 13). This increases the load on the right ventricle, which must pump blood through the now partially constricted pulmonary vessels, and leads to small airway obstructive disease. As edema worsens, the fluid accumulates within the interstitium and finally within the alveoli. As lung function deteriorates and blood is oxygenated poorly, myocardial oxygen debt leads to further cardiac deterioration. The heart may become energy-deprived owing to its increased demand for oxygen at a time when decreased oxygen enters the blood. In addition, energy starvation leads to further deterioration of both systolic and diastolic function.

HEART FAILURE

The clinical entity of *heart failure* is observed when the patient manifests clinical signs. These are commonly related to exercise intolerance[45, 46] or altered renal function[47] or both and result when tissue perfusion declines to a level incompatible with normal organ function. The mechanism for reduced exercise tolerance arises from inadequate perfusion of working muscles, or from maldistribution of perfusion within the working muscle. Either or both of these responses are mediated over a complex neuroendocrine response "designed" to protect the animal from hemorrhage or dehydration over a relatively short time.[20, 40, 46]

A cascade of events lead to congestive heart failure.[46, 48-51] Because of a diseased heart (e.g., mitral regurgitation, dilated cardiomyopathy), there is a fall, albeit slight, in cardiac output ($\dot{Q}$). This fall leads to a slight reduction in systemic arterial pressure, to reduced stretching of high-pressure baroreceptors in the aorta and carotid sinus, and to decreased numbers of afferent volleys to the medulla, indicating to the medulla that blood pressure is too low. The medulla then sends efferent volleys to increase the heart rate (i.e., it decreases vagal restraint on the sinoatrial node) and to constrict arterioles and veins (via stimulation of vascoconstrictor alpha$_1$-adrenergic receptors). The fall in cardiac output also leads to a reduction, albeit small, in renal blood flow and associated delivery of sodium chloride to the renal juxtaglomerular apparatus (JGA). This fall in sodium delivery causes the JGA to release renin. Renin causes inactive circulating angiotensinogen to be converted, predominantly in the liver, to angiotensin I. Relatively inactive angiotensin I is converted, mainly in the lung but also in many other organs, to angiotensin II. Angiotensin II initiates the following events[36, 48-54] (Fig. 11–4):

1. Stimulation of vascular smooth muscle, resulting in constriction of arteries, arterioles, and veins, which offers increased resistance to flow from LV to capillaries and reduced blood storage capacity of veins;
2. Release of vasopressin (antidiuretic hormone) from the pituitary gland, which causes reduction in urine production and further stimulation of vascular smooth muscle (Fig. 11–5);
3. Increased thirst with increased water consumption, expansion of blood volume, and further increase in pulmonary capillary pressure;
4. Decreased norepinephrine uptake from preganglionic sympathetic synapses, resulting in an increase in circulating norepinephrine levels, which (a) constricts and stimulates vascular smooth muscle, further

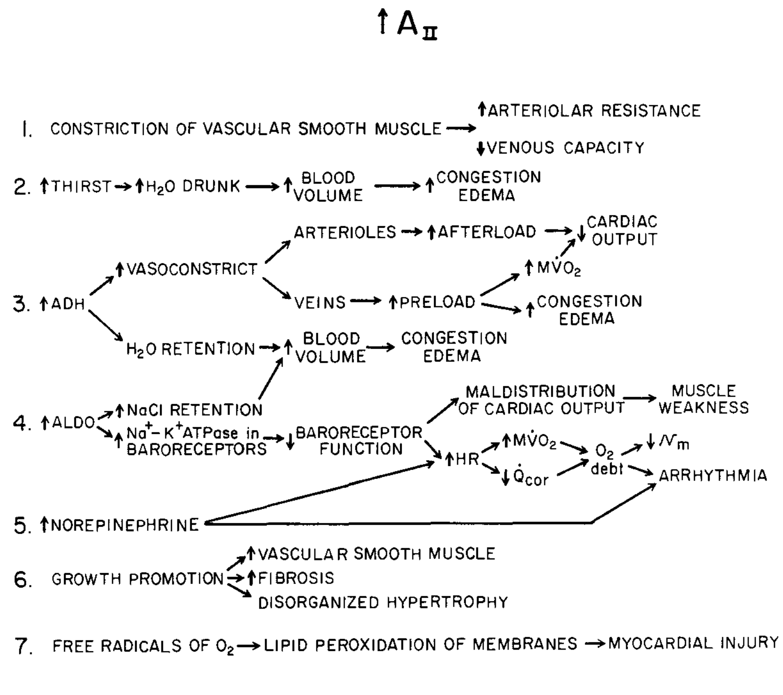


FIGURE 11–4

Summary of some of the principal effects of angiotensin-II (A_{II}) that lead to cardiovascular and renal deterioration. The sum total of these effects results in increased LV afterload, worsening of edema, hypertrophy, hyperplasia of vascular smooth muscle and the myocardium, cell membrane injury, and malfunctioning of high-pressure baroreceptors. HR, heart rate; V_m, velocity of circumferential fiber shortening; $M\dot{V}O_2$, myocardial oxygen utilization; $\dot{Q}_{cor}$, cardiac blood flow.

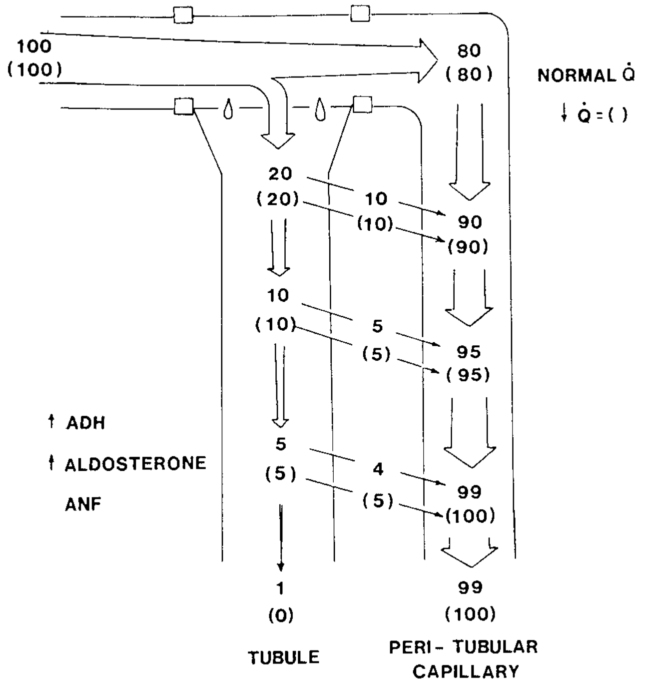


FIGURE 11–5

Example of how increased quantities of ADH and aldosterone cause the renal tubules to retain excess quantities of salt and water. Figures in parentheses are below-normal values representing those that occur with heart failure. Increased amounts of secreted ADH and aldosterone during heart failure trigger salt and water reabsorption in the distal tubules. Atrial natriuretic peptide *(ANF)* would normally counter the effects of increased ADH and aldosterone. However, this effect of ANF is overwhelmed by the surge of antidiuretic and antinatriuretic hormones (i.e., ADH and aldosterone). Furthermore, chronic left atrial distention may decrease the quantity of ANF secreted. Normally, the distal tubules only reabsorb 4 of the 5 units of provisional urine entering them from the loop of Henle. However, with increased ADH and aldosterone secretion in heart failure, nearly all of the provisional urine is reabsorbed, resulting in oliguria or anuria. Q̇, cardiac output.

increasing afterload; (b) increases heart rate,[55, 56] which both increases myocardial oxygen demand and decreases myocardial blood flow and oxygen delivery, thereby increasing myocardial oxygen debt and potentially provoking rhythm disturbances; and (c) promotes "down-regulation" (decreased numbers) of β_1-adrenergic receptors,[18] thus blunting the patient's ability to respond adequately with potentially life-saving "fight or flight" mechanisms;

5. Promotion of vascular smooth muscle growth, leading to arteriolar narrowing and myocardial hypertrophy;

6. Production of free oxygen radicals by macrophages and neutrophils, leading to lipid peroxidation of cell membranes, cell death, and replacement by fibrosis;

7. Production of aldosterone by the adrenal medulla, which initiates the following events: (a) NaCl retention by the distal convoluted tubules, decrease in urine production, increase in blood volume, and further elevation of vascular pressures and edema, and (b) loading of high-pressure baroreceptors with Na^+-K^+ ATPase (this interferes with those receptors[55, 56] sending appropriate afferent information to the medulla and results in decreased vagal efferent traffic and consequent tachycardia, leading to increased myocardial oxygen demand and decreased myocardial oxygen delivery, with further oxygen debt and energy starvation).

RENAL CONSEQUENCES IN HEART FAILURE

Although increased levels of aldosterone and ADH may account for decreased urine production (see Fig. 11–5), there is still an extremely important "*third factor*" responsible for renal sodium and water retention[57] (Fig. 11–6). Normally, for every 100 ml of plasma

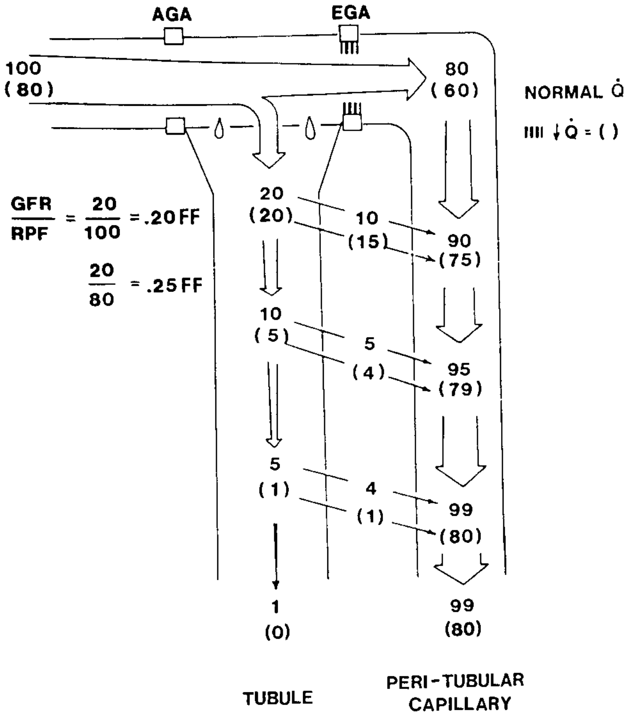


FIGURE 11–6

Example of how *increased filtration fraction*, the "third factor," causes reabsorption of extra amounts of salt and water *independent* of the presence or absence of increased quantities of ADH and aldosterone. Values in parentheses are below-normal values and represent the pathophysiologic abnormality that constitutes "third factor." In this illustration, glomerular filtration is sustained (20 ml) because of constriction of efferent glomerular arterioles *(EGA)* and dilatation of afferent glomerular arterioles *(AGA)*, despite a fall in renal plasma flow *(RPF)* from 100 to 80 ml. If glomerular filtration rate *(GFR)* is sustained while RPF is reduced, then there is a decrease (from 80 to 60 ml) in postglomerular blood entering the peritubular capillary. This reduces hydrostatic pressure within that portion of the peritubular capillary and increases the amount of provisional urine (e.g., from 10 to 15 ml) that is reabsorbed from the proximal tubule to the peritubular capillary. Thus, less provisional urine (5 ml instead of 10 ml) is presented to both the loop of Henle and distal tubule. If these regions reabsorb normally (a total of 9 ml), there will be less urine made and blood volume will be augmented. Q̇, cardiac output.

flowing into the kidneys, approximately 20 ml is filtered from the glomerular capillaries into the renal tubules as provisional urine. The glomerular membrane is impermeable to protein. Therefore, the filtrate is relatively low in protein, while the 80 ml of nonfiltered plasma that continues on its path in the peritubular capillaries is protein rich. Furthermore, the fluid pressure within the tubules is relatively low, while fluid pressure within peritubular capillaries is relatively high. The gradient of oncotic pressure is greater in peritubular capillary blood than in provisional urine and favors fluid reabsorption from the tubule to the peritubular capillary. The gradient of fluid pressure (greater in the peritubular capillary than in the renal tubule) discourages reabsorption from tubule to peritubular capillary. However, oncotic forces are dominant over those of fluid pressure. Therefore, almost 50 percent of provisional urine is

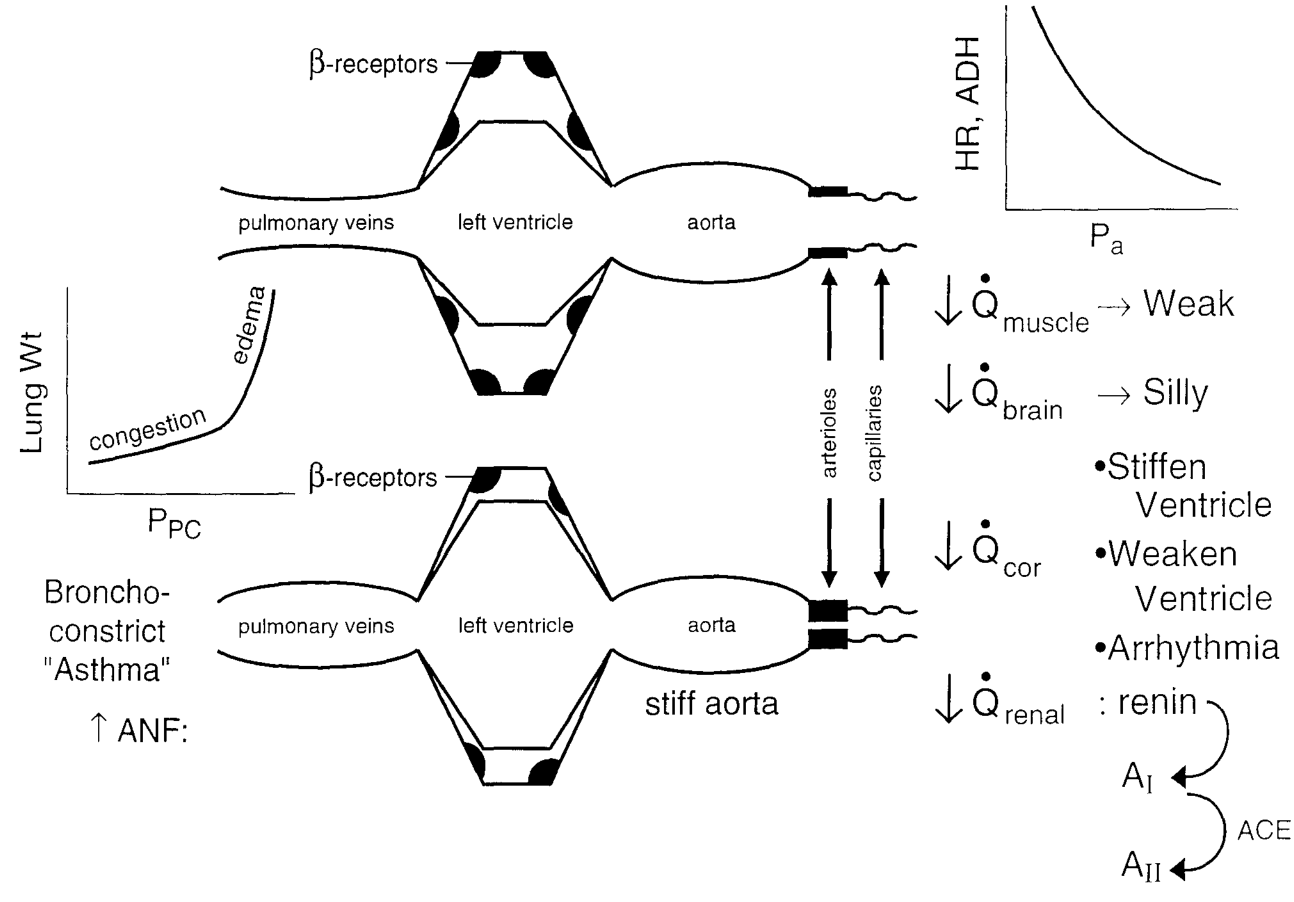


FIGURE 11-7

Diagrams illustrating cardiovascular principles. *Left side:* The normal cardiovascular circulation *(top)* is contrasted with that in heart failure *(bottom)*, comparing changes in the left ventricle, aorta, arterioles, and pulmonary veins. *Right side:* Clinical responses to reduced cardiac output ($\dot{Q}$) are depicted. For the normal state, the pulmonary veins are semicollapsed because the LV sucks blood from them during diastole. Pulmonary venous pressure is therefore low. The aorta is compliant, and distended because the LV pumps blood into it. Systemic arterial pressure is high, arterioles are normally dilated, and there are numerous myocardial β_1-receptors to which norepinephrine binds, causing the ventricle to contract more forcefully when stimulated (β_1-receptors are represented by black semicircles). Because pulmonary venous pressure and thus pulmonary capillary pressures are low, the lungs are neither edematous nor congested, and lung weight is also low.

Changes with heart failure include (1) LV dilation with its free wall thinned due to increased filling force; (2) reduced numbers (i.e., "down regulation") of myocardial β_1-adrenergic receptors due to elevated circulating catecholamine levels; (3) elevated pulmonary venous and capillary pressure; and (4) arteriolar constriction and reduced aortic compliance due to vascular smooth muscle stimulation resulting from increased plasma norepinephrine, vasopressin, and angiotensin II concentrations. This damming-up of blood with the pulmonary circuit makes the lung congested, edematous, and heavy.

Graph of lung weight vs. pulmonary capillary pressure (P_{PC}): This shows lung weight increasing dramatically as pulmonary edema appears. Dilation of the pulmonary veins elicits a bronchoconstrictive reflex. Left atrial dilation (not shown) increases the release of atrial natriuretic peptide or factor *(ANF)*, the substance that prevents the synthesis and effects of angiotensin-II, although ANF release may be dulled by chronic left atrial distention.

To the right of the diagram is shown the constellation of clinical responses characterizing heart failure. At the top right is a graph plotting release of ADH and heart rate *(HR)* as a function of systemic arterial pressure (P_a). As systemic arterial pressure rises, both heart rate and ADH increase. Reduced blood flow *($\dot{Q}$)* to the muscles, brain, heart *($\dot{Q}_{cor}$)*, and kidneys *($\dot{Q}_{renal}$)* results in corresponding responses of weakness, behavior changes, increased myocardial stiffness, decreased myocardial contractility, arrhythmia, and renin production, respectively. Renin ultimately results in angiotensin-II production and other pathologic responses (see also Fig. 11–4).

reabsorbed from the proximal convoluted tubule by surrounding peritubular capillaries.

FILTRATION FRACTION AS THE THIRD FACTOR

Compensatory renovascular changes account for the oliguria and polydipsia observed in congestive heart failure. These physiologic mechanisms result in changes that also present the circulation with fluid to be distributed, according to hydrostatic and oncotic forces, as ascites, pulmonary edema, or pitting edema. When renal plasma flow decreases and the renin-angiotensin-aldosterone axis is activated, efferent glomerular arterioles constrict and afferent glomerular arterioles dilate. This causes the volume of glomerular filtrate to remain nearly constant despite a drop in renal plasma flow. Thus, the *filtration fraction* (the ratio of volume of glomerular filtration to renal plasma flow), which is normally 0.2, elevates to as high as 0.3. This means that the volume of renal plasma flow destined for peritubular capillaries (i.e., renal plasma flow minus glomerular filtrate) is diminished. The reduced plasma volume is richer in protein (i.e., possesses greater oncotic pressure) and also is perfusing at a lower fluid pressure (i.e., there is less of it). Thus, a relatively greater amount (by percentage as well as absolute volume) will be reabsorbed from renal tubule to peritubular capillary. This causes reduced urine volume and conservation of water and solutes when the animal may be manifesting increased water intake due to thirst precipitated by excessive angiotensin II.

HEART RATE RESPONSE TO HEART FAILURE

Heart rate increases in response to several stimuli. Due to a slight fall in systemic arterial pressure, vagal restraint on heart rate is reduced, from either decreased arterial baroreceptor stretching or diminished function of those baroreceptors. Heart rate variability, termed respiratory sinus arrhythmia, decreases. Elevated circulating catecholamine concentrations also increase heart rate. This is injurious for two reasons: (1) increased heart rate increases myocardial oxygen consumption at a time when blood oxygenation may be impaired due to pulmonary congestion and edema, and (2) increasing heart rate shortens diastole, the period when coronary blood flow delivers oxygen to the myocardium,[58, 59] with resultant decrease in myocardial oxygen supply.

NEUROENDOCRINE RESPONSES

Increased levels of circulating catecholamines and heightened sympathetic stimulation also result in decreased arterial vasodilatory reserve to working muscles. This either reduces blood supply to those muscles or produces maldistribution of blood within the muscles, which causes decreased exercise capacity and muscular weakness. Complex and still poorly understood neuroendocrine responses to reduced cardiac output initiate a constellation of clinical signs (e.g., polydipsia, oliguria, vasoconstriction, tachycardia, muscular weakness, and exercise intolerance) (Figs. 11–4, 11–7). Together, these changes coupled with those previously described result in the clinical syndromes of heart failure or congestive heart failure. Basic cardiovascular principles relating neuroendocrine, hemodynamic, and clinical aspects of heart failure are illustrated in Figure 11–7.

REFERENCES

1. Parmley WW, Chatterjee K. Principles in the management of congestive heart failure. *In* Parmley WW, Chatterjee K (eds): Cardiology. Philadelphia, JB Lippincott, 1988, p 1
2. Braunwald E. Pathophysiology of heart failure. *In* Braunwald E (ed): Diseases of the Heart. 4th ed. Philadelphia, WB Saunders, 1992, p 393
3. Hackel D, Ratliff N, Mikat E. The heart in shock. Circ Res 35:805, 1974
4. Alpert NR, Gordon MS. Myofibrillar adenosine triphosphatase activity in congestive heart failure. Am J Physiol 202:940, 1962
5. Chandler BM, Sonnenblick EG, Spann FR, Pool PE. Association of depressed myofibrillar adenosine triphosphates and reduced contractility in experimental heart failure. Circ Res 21:717, 1967
6. Conway G, Heazlitt RA, Montag J, Mattingly SR. The ATPase activity of cardiac myosin from failing and hypertrophied hearts. J Mol Cell Cardiol 7:817, 1975
7. Feldman MD, Copelas L, Gwathmey JK, et al. Deficient production of cyclic AMP: Pharmacologic evidence of an important cause of contractile dysfunction in patients with end-stage heart failure. Circulation 75:331, 1987
8. Furchgott RF, Lee KS. High energy phosphates and the force of contraction of cardiac muscle. Circulation 24:416, 1961
9. Kammermeier H, Schmidt P, Jungling E. Free energy change of ATP hydrolysis: A causal factor of early hypoxic failure of the myocardium. J Mol Cell Cardiol 14:267, 1982
10. Peyton RB, Jones RN, Attarian D, et al. Depressed high-energy phosphate content in hypertrophied ventricles of animal and man: The biologic basis for increased sensitivity to ischemic injury. Ann Surg 196:278, 1982
11. Pool PE, Spann JF Jr, Buccino RA, et al. Myocardial high energy phosphate stores in cardiac hypertrophy and heart failure. Circ Res 21:365, 1967
12. Braunwald E, Ross J Jr, Sonnenblick EH. Mechanisms of Contraction of the Normal and Failing Heart. 2nd ed. Boston, Little, Brown, 1976
13. Covell JW, Ross J, Sonnenblick EH, Braunwald E. Comparison of the force-velocity relation and the ventricular function curve as measures of the contractile state of the intact heart. Circ Res 19:364, 1966
14. Hanson J, Lowy J. Molecular basis of contractility in muscle. Br Med Bull 21:264, 1965
15. Huxley HE. Structural arrangements and contraction mechanism in striated muscle. Proc R Soc Lond (Biol) 160:442, 1964

16. Levine HJ, Briman MA. Force-velocity relations in intact dog heart. J Clin Invest 43:1383, 1964
17. Zelis R, Amsterdam EA, Mason DT. "Isometric" V_{max} as an index of contractility independent of series elastic and fiber shortening: Implications concerning pressure-velocity data in myocardial fibrosis, valvular regurgitation, ventricular aneurysm and ventricular septal defect. Circulation 44(suppl 2):89, 1971
18. Boettcher D, Vatner S, Heydrick G. Extent of utilization of the Frank-Starling mechanisms in conscious dogs. Am J Physiol 234:H338, 1978
19. Grossman W, Hayes F, Paraskos JA, et al. Alterations in preload and myocardial mechanics in the dog and in man. Circ Res 31:83, 1972
20. Katz AM. Physiology of the Heart. New York, Raven Press, 1977
21. Katz AM. Regulation of cardiac muscle contractility. J Gen Physiol 50:Suppl:185, 1967
22. Katz AM. Regulation of myocardial contractility, 1958–1983: An odyssey. J Am Coll Cardiol 1:42, 1983
23. Wikman-Coffelt J, Mason DT. Mechanism of decreased contractility in chronic hemodynamic overload. *In* Mason DT (ed). Advances in Heart Disease, I. New York, Grune & Stratton, 1977, p 491
24. Sonnenblick EH, Ross J Jr, Spotnitz HM, et al. The ultrastructure of the heart in systole and diastole: Changes in sarcomere length. Circ Res 21:423, 1967
25. Braunwald E. Control of myocardial oxygen consumption. Am J Cardiol 27:416, 1971
26. Coleman HN, Sonnenblick EH, Braunwald E. Myocardial oxygen consumption associated with external work: The Fenn effect. Am J Physiol 217:291, 1969
27. Duling B. Oxygen, metabolism, and microcirculatory regulation. *In* Kaley G, Altura BM (eds): Microcirculation. Vol II. Baltimore, University Park Press, 1977, p 401
28. Haugaard N, Haugaard ES, Lee NH, Horn RS. Possible role of mitochondria in regulation of cardiac contractility. Fed Proc 28:1657, 1969
29. Zak R, Martin AF, Reddy MK, Rabinowitz M. Control of protein balance in hypertrophied cardiac muscle. Circ Res 38 (Suppl 10):146, 1976
30. Roberts JT, Wearn JT. Quantitative changes in the capillary-muscle relationship in human hearts during normal growth and hypertrophy. Am Heart J 21:617, 1941
31. Wollegberger A. Losses in mitochondrial mass, structure, and metabolic capacity in the hypertrophied heart prior to failure. *In* Memorias del IV Congreso Mundial de Cardiologia. Vol 5. Mexico City, Comite Editorial de IV Congreso Mundial de Cardiologia, 275, 1963
32. Meerson FZ. On the mechanism of compensatory hyperfunction and insufficiency of the heart. Cor Vasa 3:161, 1961
33. Meerson FZ, Pshennikova MG. The effect of myocardial hypertrophy on the contractile function of the heart. Byul Eksper Biol Med 59:36, 1965
34. Rabinowitz M. Protein synthesis and turnover in normal and hypertrophied heart. Am J Cardiol 31:202, 1973
35. Wikman-Coffelt J, Salel AF, Mason DT. Differential responses of canine myosin ATPase activity and tissue gases in the pressure-overloaded ventricle dependent upon degree of obstruction: Mild versus severe pulmonic and aortic stenosis. Recent Adv Stud Cardiol Struct Metab 12:367, 1978
36. Wilson J, Lancoe V, Frey M, Ferraro N. Arterial baroreceptor control of peripheral resistance in experimental heart failure. Am Heart J 119:1122, 1990
37. Neumann J, Schmitz W, Scholz H, et al. Increase in myocardial G-proteins in heart failure. Lancet 2:936, 1988
38. Hamilton MA, Stevenson LW, Luu M, Walden JA. Altered thyroid dysfunction in elderly hospitalized patients. Effect of age and severity of illness. Arch Intern Med 150:1249, 1990
39. Gaasch WH, Levine HJ, Quinnes MA, et al. Left ventricular compliance mechanisms and clinical implications. Am J Cardiol 38:645, 1976
40. Katz AM. Biochemical "defect" in the hypertrophied and failing heart: Deleterious or compensatory? Circulation 47:1076, 1973
41. Wexler LF, Lorell BH, Momomura S, et al. Enhanced sensitivity to hypoxia-induced diastolic dysfunction in pressure-overload left ventricular hypertrophy in the rat: Role of high-energy phosphate depletion. Circ Res 62:766, 1988
42. Guyton A. Pulmonary alveolar capillary interface and interstitium. *In* Fishman A, Hecht H (eds): The Pulmonary Circulation and Interstitial Space. Chicago, University of Chicago Press, 1969
43. Moore DP, Weston A, Hughes JMB, et al. Bronchial hyperresponsiveness in heart failure; Letter. N Engl J Med 328:1424, 1993
44. Weiss S, Robb G. Cardiac asthma (paroxysmal cardiac asthma) and the syndrome of left ventricular failure. JAMA 100:1841, 1933
45. Mason D, Zelis R, Longhurst J, Lee G. Cardiocirculatory responses to muscular exercise in congestive heart failure. Prog Cardiovasc Dis 19:475, 1977
46. Zelis R, Sinoway LI, Musch TI, et al. Regional blood flow in congestive heart failure: Concept of compensatory mechanisms with short and long time constants. Am J Cardiol 62:2E, 1988
47. Barger A, Muldowney F, Lubowitz S. Role of the kidney in the pathogenesis of congestive heart failure. Circulation 20:273, 1959
48. Francis GS, Goldsmith SR, Levine TB, et al. The neurohumoral axis in congestive heart failure. Ann Intern Med 101:370, 1984
49. Laragh J. Hormones and the pathogenesis of congestive heart failure: Vasopressin, aldosterone, and angiotensin. Circulation 25:1015, 1962
50. Mancia G. Sympathetic activation in congestive heart failure. Eur Heart J 11(Suppl A):3, 1990
51. Packer M, Gottlieb S, Blum M. Immediate and long-term pathophysiologic mechanisms underlying the genesis of sudden death in patients with congestive heart failure. Am J Med 82:504, 1987
52. Daemen JJ, Lombardi DM, Bosman FT, Schwartz SM. Angiotensin II induces smooth muscle cell proliferation in the normal and injured rat arterial wall. Circ Res 68:450, 1991
53. Thomas JA, Marks BH. Plasma norepinephrine in congestive heart failure. Am J Cardiol 41:233, 1978
54. Francis GS. Neurohumeral mechanisms involved in congestive heart failure. Am J Cardiol 55:15A, 1985
55. Cowley A, Laird J, Guyton A. Role of baroreceptor reflex in the daily control of arterial pressure and other variables in the dog. Circ Res 32:564, 1973
56. Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. N Engl J Med 285:877, 1971
57. Hamlin RL. Pathophysiology of heart failure. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 159
58. Berne R. Regulation of coronary blood flow. Physiol Rev 44:1, 1964
59. Gregg DE. Coronary circulation in the anesthetized dog. *In* Marchette G, Taccarde B (eds): Coronary Circulation and Energetics of the Myocardium. Basel, S. Karger, 1967, p 54

12

Management of Heart Failure: Principles of Treatment, Therapeutic Strategies, and Pharmacology

DAVID SISSON
MARK D. KITTLESON

Many different diseases can cause signs of heart failure. Accordingly, there are numerous approaches to therapy, depending on the unique circumstances of each patient. The ideal treatment is to achieve a cure, but as this is usually not possible, treatment goals are to improve the quality and length of life. Toward this end, management efforts engage in a number of strategies intended to relieve congestion, control excess sodium and water retention, improve cardiac pumping function, or reduce cardiac workload. Specific goals of treatment decisions are facilitated by knowledge of pharmacology, the hemodynamic effects of drugs, the nature and prevalence of adverse drug reactions, short- and long-term efficacy, and the effect of drugs on quality of life.

PRINCIPLES OF TREATMENT

CLASSIFICATION OF PATIENTS WITH HEART FAILURE

Animals with heart failure can be categorized based on the functional disturbance(s) caused by their underlying disease. Therapy is usually directed at correcting or palliating the specific functional abnormalities responsible for the patient's clinical signs (Table 12–1).

The heart has two primary functions. One is to receive blood from the pulmonary and systemic venous reservoirs (diastolic performance); the other

TABLE 12–1
Heart Failure: The Goals of Therapy

I. Control Salt and Water Retention/Relieve Edema
Low sodium diets
Loop, thiazide, potassium-sparing diuretics
Venous and mixed vasodilators
Angiotensin converting enzyme inhibitors
Physical removal of fluid

II. Improve Pump Function
Improve diastolic filling
  Control heart rate
  Abolish arrhythmia, restore A-V synchrony
  Improve ventricular relaxation
Improve contractility
  Digitalis glycosides
  Bipyridines
  Sympathomimetic drugs
Reverse or modify myocardial and vascular remodeling
  Angiotensin converting enzyme inhibitors
  Beta-receptor blocking drugs

III. Reduce Workload
Reduce afterload, ACE inhibitors, arterial or mixed vasodilators
Reduce physical activity
Avoid environmental stressors
Weight reduction in the obese

is to propel blood in a forward direction through the pulmonary and systemic vasculature (systolic performance). Systolic dysfunction predominates in most heart failure patients, but others suffer from diseases that primarily impair diastolic performance. The general approach to treatment is greatly influenced by these distinctions, which must be clinically determined.

A number of other considerations are important in selecting therapy:

(1) The chronicity of clinical signs (acute versus chronic heart failure);
(2) The severity of the disease (mild, moderate, or severe heart failure); and
(3) The predominating clinical manifestations (congestive versus low-output heart failure, and right- versus left-sided heart failure).

For example, acute, severe congestive heart failure (CHF) is treated much more aggressively and with different drug combinations than is chronic, less severe disease.

THERAPEUTIC APPROACH TO DIASTOLIC DYSFUNCTION

Impaired cardiac filling can result from excessive pericardial restraint, obstructions to venous inflow, impaired myocardial relaxation, reduced ventricular compliance, excessive heart rates, and weak, absent, or poorly timed atrial contractions. Myocardial relaxation is an active, energy-requiring process that initiates diastolic filling.[1] The rate and extent of myocardial relaxation depend on the rate at which cytosolic calcium ions are resequestered by the sarcoplasmic reticulum. This requires adenosine triphosphate (ATP) and phosphorylation of phospholamban, which normally occurs rapidly and uniformly.

Myocardial relaxation is determined by systolic loading conditions and inherent cardiac viscoelastic properties. Increasing afterload improves relaxation up to a point, but excessive afterload has an adverse effect. Hypertrophied hearts relax more slowly and less uniformly than normal hearts. When the ventricle is diseased, the onset of relaxation is often delayed and the rate and extent of relaxation are reduced, either globally or to varying degrees in different regions of the heart.

Ventricular compliance is the ability of the heart to fill passively and is usually measured at the end of diastole when the ventricle is relaxed. This concept is best explained by a graphic display of the ventricle's end-diastolic pressure-volume relationship, the slope of which defines compliance at any given level of preload (Fig. 12–1).[2, 3] Given the same end-diastolic volume, end-diastolic pressure will be higher if the ventricle is stiffer (less compliant) than a normal ventricle. Ven-

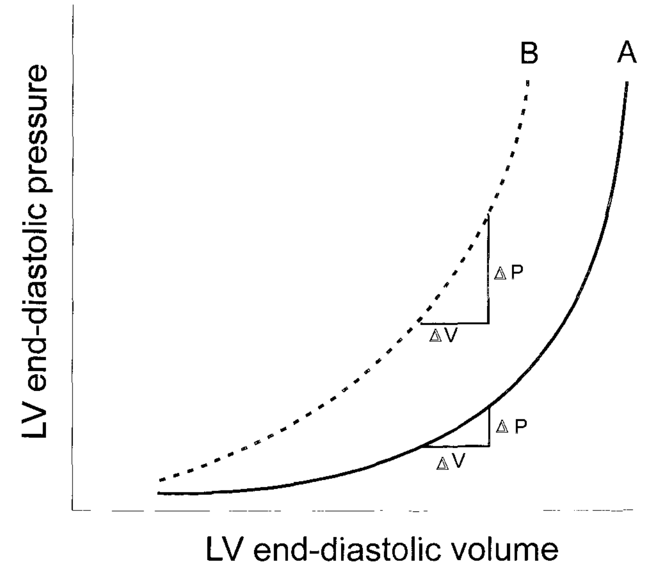


FIGURE 12–1

The left ventricular end-diastolic pressure-volume relationship for any patient can be expressed as an exponential curve. *Myocardial stiffness* refers to the ability of the myocardium to resist filling during diastole. Conversely, *myocardial compliance* refers to the ability of the myocardium to be stretched during diastole. The slope of the curve at any point is a measure of ventricular stiffness at that particular volume. The greater the ventricular volume, the stiffer the chamber wall. In a clinical context, myocardial stiffness increases when the ventricle dilates, when the wall hypertrophies, or when myocardial fibrosis is present. Notice that as the left ventricle (LV) fills (i.e., the LV end-diastolic volume increases), the slope of the curve increases, indicating that the left ventricle becomes progressively stiffer (less compliant). This is evident in patient 'B'—it takes greater pressure to achieve the same end-diastolic volume compared with patient 'A.' The difference in LV end-diastolic pressure between patients 'A' and 'B' becomes even more pronounced as the LV end-diastolic volume increases. ΔV, change in volume; ΔP, change in pressure.

tricular compliance is determined by the volume and geometry of the chamber as well as the thickness and tissue characteristics (composition) of its walls.[3, 4] Compliance failure can occur with myocardial or endocardial fibrosis, or with ventricular hypertrophy.[4] Feline hypertrophic cardiomyopathy (HCM) is characterized by concentric hypertrophy of the left ventricle, impaired myocardial relaxation, and reduced left ventricular compliance[5–9] (see chapter 28). As a result, left ventricular (LV) diastolic and left atrial pressures increase, and pulmonary edema develops in some cases.

IMPLICATIONS FOR THERAPY. The most effective treatment of patients with reduced compliance and impaired ventricular relaxation is to resolve the underlying disorder. Resolution of LV hypertrophy can be achieved in patients with systemic hypertension by effectively reducing arterial blood pressure. For all practical purposes it is impossible to resolve the extensive myocardial fibrosis observed in cats with restrictive cardiomyopathy (RCM). On rare occasions, ventricular hypertrophy due to hypertrophic cardiomyopathy resolves with treatment. More often, therapy must be directed at those compensatory responses and coexisting conditions that further limit diastolic filling. These include excessively fast heart rates, weak or poorly timed atrial contractions, sodium and water retention, venous constriction, and diminished systolic performance of the heart.[10] Optimization of preload, control of heart rate, and maintenance of sinus rhythm are crucial to the successful treatment of many patients with diastolic myocardial dysfunction, particularly when the primary disorder cannot be resolved. Impaired ventricular filling can sometimes be augmented by drugs that improve myocardial relaxation (positive lusitropy).

Beta-adrenergic receptor blocking drugs and calcium channel blocking agents are commonly prescribed for HCM, but for somewhat different reasons.[5–9, 11] Beta-blockers effectively reduce excessive heart rates, thereby improving diastolic filling; they can also diminish or eliminate dynamic LV outflow tract obstruction and associated mitral regurgitation.[7, 8] As a result, ventricular performance may improve. Diltiazem is reported to improve myocardial relaxation in cats with HCM and may also cause regression of LV hypertrophy in some cats.[5, 6] Diltiazem also tends to slow resting heart rate, but this effect is not as reliable or as dramatic as that observed with β-blockers when sympathetic tone is high.[6] Diltiazem does not appear to abolish dynamic obstruction as reliably as do β-blockers.

Pulmonary edema is most effectively treated with furosemide. Cats with refractory pulmonary edema due to HCM may benefit from combined treatment with furosemide and a venous vasodilator, such as nitroglycerin. However, when filling is impaired, excessive preload reduction resulting from inappropriately high doses of diuretics can precipitate signs of low-output heart failure.[12] Arterial vasodilating drugs should be avoided in HCM, as they can precipitate systemic arterial hypotension and worsen dynamic obstruction.[6] Angiotensin-converting enzyme (ACE) inhibitors appear to be efficacious in relieving signs of CHF without adversely affecting hemodynamics. Positive inotropic drugs can also worsen dynamic obstruction.

In cats with restrictive cardiomyopathy, the principal functional deficit is compliance failure, although reduced systolic contractile indices are sometimes present as well[13] (chapter 28). Treatment options are limited. Diuretics and a low-salt diet are used to control congestion and edema.[3, 4, 12] Positive inotropic drugs may be useful when concomitant systolic pump failure is present. Reduction of tachycardia may improve diastolic filling. There is some evidence that ACE inhibitors and aldosterone antagonists may reduce myocardial fibrosis, but their value in affected cats, if any, is unknown.[14]

Pericardial disorders such as pericardial effusion and constrictive pericarditis cause signs of heart failure by impairing diastolic filling. Cardiac tamponade from pericardial effusion is acutely managed by pericardiocentesis (chapter 29). When pericardial and epicardial fibrosis restrain cardiac diastolic filling, as with constrictive pericarditis, surgical removal of the parietal and/or visceral pericardium is required. In atrioventricular valve stenosis or mass lesions that obstruct venous inflow, surgery or balloon dilation of the offending lesion is usually required. When definitive treatment cannot be accomplished, clinical improvement often can be realized using diuretics and drugs to control heart rate.

THERAPEUTIC APPROACH TO SYSTOLIC DYSFUNCTION

Impaired systolic ejection can result from (1) primary myocardial failure (e.g., dilated cardiomyopathy); (2) chronic volume overload (e.g., chronic mitral valve insufficiency or a congenital shunt [atrial septal defect, ventricular septal defect, patent ductus arteriosus]); or (3) chronic pressure overload (e.g., outflow tract obstruction or arterial hypertension). Reduced myocardial contractility is the initial and principal abnormality in patients with dilated cardiomyopathy. With chronic pressure or volume overload, myocardial failure eventually develops secondary to some other cardiac disorder, such as valvular stenosis or insufficiency. In these patients, signs of congestive heart failure can develop with no or only modest reductions in myocardial contractility. A thorough understanding of normal systolic function provides the basis for assessing systolic dysfunction and its therapeutic implications.

The relationship between wall stress and ventricular volume in a normal dog is depicted in Figure 12–2. During diastole, the ventricle fills to a certain end-diastolic volume, with accompanying end-diastolic wall stress. During isovolumic systole, the mitral and aortic valves are closed and left ventricular pressure rises, but left ventricular volume and wall thickness do not change. This results in increased wall stress. Ejection begins when the aortic valve opens. During ejection, pressure increases a small amount and then declines as chamber diameter decreases and the wall thickens. This results in decreasing wall stress throughout ejection. During isovolumic relaxation, wall stress decreases while left ventricular volume stays the same.

The relationship of contractility to systolic wall stress (afterload) and ventricular volume in a normal dog is illustrated in Figure 12–3. If systolic intraventricular pressure is increased, systolic wall stress (afterload) increases, resulting in decreased fiber shortening. End-systolic volume increases because the chamber no longer can empty as completely as it did before. When a line is drawn connecting the end-systolic wall stress-volume points from each loop, its slope (E_{max}) and x-axis intercept (V_o) define myocardial contractility.[15]

Primary Myocardial Failure

Taurine deficiency cardiomyopathy in cats and idiopathic dilated cardiomyopathy of large-breed dogs are examples of diseases causing reduced myocardial contractility.[13, 16] When myocardial contractility is decreased, E_{max} flattens and V_o shifts to the right.[17] For any given end-systolic wall stress, end-systolic volume is increased because the weakened muscle fibers cannot shorten as far. As a result, stroke volume declines. The body compensates for decreased stroke volume by increasing heart rate and by increasing preload via renal salt and water retention. Fluid retention increases end-diastolic pressure and end-diastolic volume, thereby increasing stroke volume (Frank-Starling law).

Increased end-diastolic volume causes the normal ventricular wall to stretch around a larger than normal chamber, and the ventricular wall becomes thinner. The result is increased end-diastolic wall stress. When end-diastolic volume and wall stress increase, the sarcomeres within the myocytes replicate *in series*, and wall thickness increases in proportion to the change in chamber size.[18] This type of cardiac hypertrophy is called *eccentric* or *volume overload hypertrophy*. Eccentric hypertrophy allows a moderately impaired heart to eject a normal stroke volume despite diminished myocardial contractility.

A wall stress-volume loop from a patient with severe myocardial failure (dilated cardiomyopathy [DCM]) is

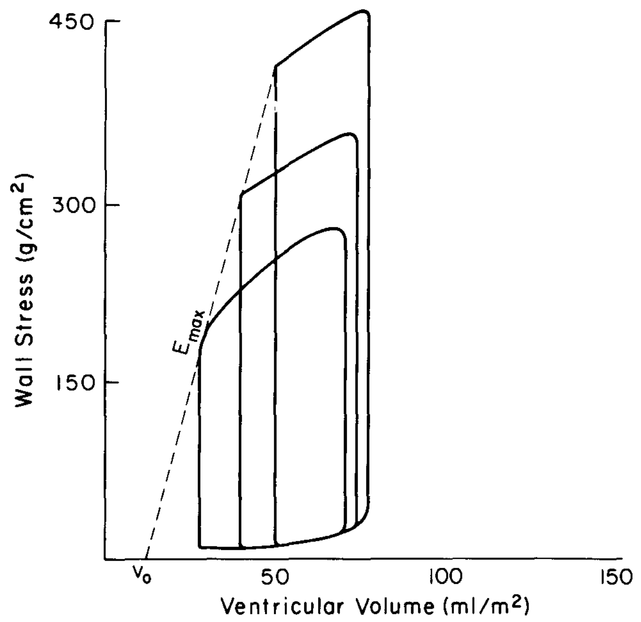


FIGURE 12–3

Wall stress-volume loops before and after the administration of an agent that constricts systemic arterioles. As end-systolic pressure (hence wall stress) increases, heart muscle contraction is reduced at end-systole. This causes an increase in end-systolic volume and a decrease in stroke volume. The slope (E_{max}) and x intercept (V_o) of the line connecting the end-systolic wall stress-volume points define myocardial contractility. (From Kittleson ME. Management of heart failure: Concepts, therapeutic strategies, and drug pharmacology. *In* Fox PR [ed]: Canine and Feline Cardiology. 1st ed. New York, Churchill Livingstone, 1988, p 179.)

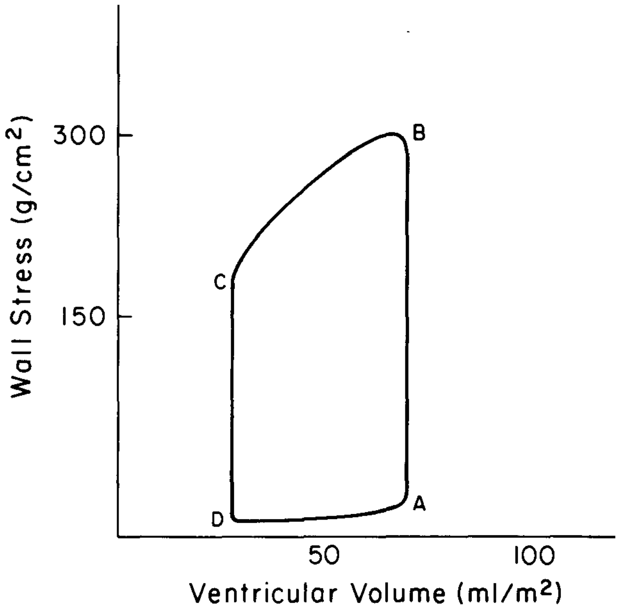


FIGURE 12–2

Normal wall stress-volume loop for the left ventricle. *A*, End-diastole and the point at which the mitral valve closes. *A-B*, Isovolumic systole. *B*, The onset of ejection and opening of the aortic valve. *B-C*, Ejection; the volume of *B* minus the volume of *C* is the *stroke volume*. *C*, End-systole and closing of the aortic valve. *C-D*, Isovolumic relaxation. *D*, Mitral valve opening. *D-A*, Ventricular filling. (From Kittleson ME. Management of heart failure: Concepts, therapeutic strategies, and drug pharmacology. *In* Fox PR [ed]: Canine and Feline Cardiology. 1st ed. New York, Churchill Livingstone, 1988, p 178.)

depicted in Figure 12–4. In this example, end-diastolic volume index (EDVI) is increased from the normal value of less than 100 ml/m² of body surface area to 250 ml/m². End-systolic volume index (ESVI) is increased from a normal value of less than 30 ml/m² to 220 ml/m². The mitral valve annulus has been enlarged by left ventricular dilation, resulting in mild mitral regurgitation. This patient's total left ventricular stroke volume index (EDVI-ESVI) is 30 ml/m². However, 20 percent of that stroke volume index (6.0 ml/m²) is ejected into the left atrium owing to the mitral regurgitation. Consequently, the forward stroke volume index (that amount ejected into the aorta) is only 24 ml/m², compared with a normal stroke volume index of 30 to 50 ml/m². Because of the large end-diastolic volume and the stiffer than normal myocardium, end-diastolic pressure is increased, causing pulmonary edema. Increased end-diastolic pressure and chamber dilation have increased end-diastolic wall stress, maximally stretching the sarcomeres at end-diastole, stimulating further sarcomere replication and

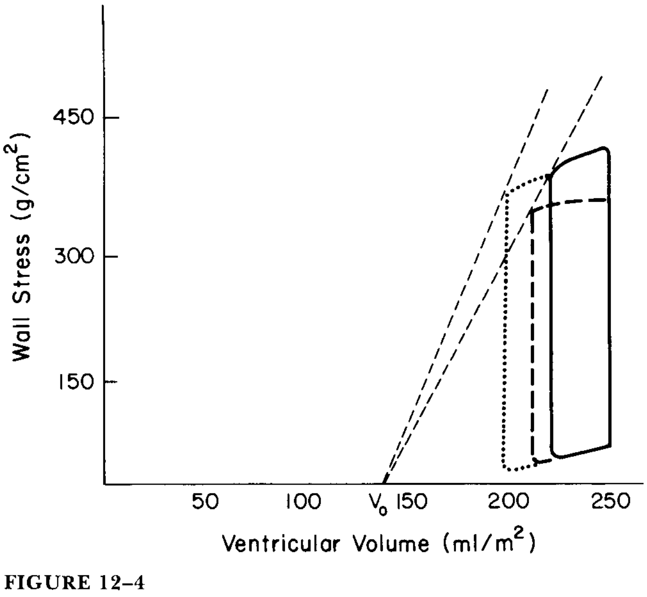


FIGURE 12–4

Wall stress volume loops from a dog with severe myocardial failure. The solid line represents baseline values. End-diastolic ventricular volume is increased because of renal salt and water retention, leading to eccentric hypertrophy. End-systolic volume is increased because of decreased myocardial contractility and increased systolic wall stress (afterload). Compared with Figure 12–3, E_{max} (the slope of the line defining contractility) is flatter than normal, and V_o (the x intercept of that line) is shifted to the right (i.e., myocardial contractility is decreased). The dotted line represents a portion of the new loop formed after administration of a positive inotrope; E_{max} becomes steeper, resulting in a decrease in end-systolic volume and, therefore, increase in stroke volume. The dashed line shows a portion of a new loop that forms after the administration of an arteriolar dilator. E_{max} and V_o do not change, but systolic wall stress decreases because of the resultant decrease in blood pressure. End-systolic volume decreases due to the increased stroke volume. (From Kittleson ME. Management of heart failure: Concepts, therapeutic strategies, and drug pharmacology. *In* Fox PR [ed]: Canine and Feline Cardiology. 1st ed. New York, Churchill Livingstone, 1988, p 182.)

chamber dilation. As myocardial contractility continues to decline, the compensatory process of myocardial hypertrophy fails, the ratio of wall thickness to chamber size declines, systolic wall stress increases, and heart failure occurs.

IMPLICATIONS FOR THERAPY. Several different strategies can be employed to treat primary myocardial failure. The ideal treatment would restore myocardial contractility to normal, as occurs when taurine is provided to cats with taurine deficiency.[16] The rationale for using positive inotropic drugs is that functional improvement should occur if the drug is sufficiently potent, and if the surviving myocytes can respond. Positive inotropes such as dobutamine and milrinone are often used successfully to treat humans with acute, decompensated myocardial failure.[19] These drugs improve but do not normalize myocardial contractility (Fig. 12–4). Unfortunately, survival times are diminished in humans treated chronically with β_1-agonists or phosphodiesterase inhibitors, in part because of an increased rate of sudden death.[19, 20] For this reason, these drugs are not used for chronic therapy except in special circumstances. Digoxin, which has no effect on overall mortality, is often used chronically to improve contractility, to control supraventricular tachycardias, and to modulate some of the autonomic changes evoked in heart failure.[13, 19]

Current strategies for the long-term management of chronic myocardial failure emphasize drugs that reduce afterload, decrease cardiac venous return, or modify the systemic neurohormonal responses elicited by declining cardiac function (Figs. 12–4, 12–5).[19] This approach allows cardiac output to increase without increasing myocardial work and oxygen consumption, while reducing diastolic intraventricular pressures. Improved exercise tolerance and increased survival times have been reported.[21–24] As in other types of heart failure, diuretics are required to control congestion and edema.

Chronic Volume Overload

Mitral, aortic, and tricuspid regurgitation and left-to-right shunts, such as ventricular septal defect (VSD) and patent ductus arteriosus (PDA), cause volume overloading of the left- or right-sided heart, or both. Volume overload results in eccentric hypertrophy of the involved chambers and heart failure if severe. Repair of the lesion is preferred and is most commonly available for PDA. When repair of the defect is not an option, the goal of medical therapy is to delay the onset of heart failure, slow progression, and reduce associated clinical signs.

MITRAL REGURGITATION. Acute mitral regurgitation (MR) causes a decrease in forward stroke volume by

permitting a certain percentage of the ejected stroke volume to leak from the left ventricle (LV) back into the left atrium (LA). Decreased forward stroke volume and cardiac output stimulate sympathetic outflow and catecholamine release, thereby increasing heart rate and contractility. Decreased renal perfusion stimulates renal compensatory responses and renin release from the kidney. Within 2 to 4 days, about 50 percent of the β-receptors become desensitized to catecholamine stimulation.[25] For a time, fluid retention and the Starling mechanism help compensate for the initial decline in stroke volume. Eventually, the LV hypertrophies to accommodate the volume of blood regurgitated into the LA. End-diastolic wall stress returns to normal but the LV is now enlarged.

In patients with MR, about 50 percent of the total left ventricular stroke volume may be ejected into the LA before the aortic valve opens. This permits the LV to eject a large blood volume at relatively low pressure, with low wall stress and only modest increases in myocardial oxygen consumption. These conditions allow myocardial contractility to remain normal for prolonged periods.[26] A wall stress-volume loop from such a dog is illustrated in Figure 12–6. Since contractility is normal and systolic wall stress is relatively normal, end-systolic volume is normal.

As the mitral valve continues to degenerate and the LV continues to enlarge, an ever-increasing percentage of the stroke volume (up to 75 to 90 percent in dogs with severe MR) is ejected into the LA. Progressive enlargement of the left-sided heart is accompanied by increased wall stress and myocardial oxygen consumption. Peripheral vasoconstriction and fluid retention, evoked by neurohormonal responses to declining cardiac output, increase afterload and preload, further increasing the regurgitant volume and heart size. Diminished myocardial perfusion, myocardial fiber slippage, and excessive afterload detract from the inotropic support provided by neurohormonal activation.[27] In dogs with experimentally created MR, the extent of myocardial dysfunction can be demonstrated by administration of β-adrenergic blocking drugs.[28] Eventually, dogs with severe valvular insufficiency experience a substantial decline in myocardial contractility, as illustrated in Figure 12–6.

The severity of pulmonary congestion and the resulting clinical signs do not necessarily reflect the volume of regurgitation or the contractile state of the myocardium. Pulmonary congestion tends to develop when left atrial pressure rises sufficiently (to about 25 mmHg) to increase hydrostatic pressure in the pulmonary capillaries. Left atrial pressure is a function of left atrial compliance, the volume of blood arriving from the right-sided heart, the volume of blood that leaks

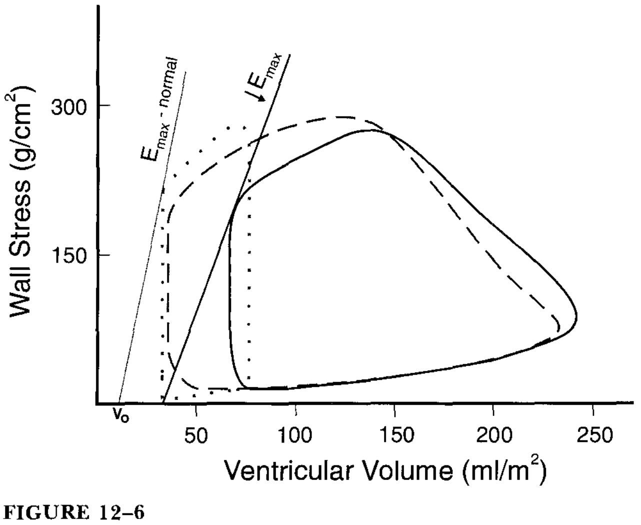


FIGURE 12–6

Left ventricular wall stress-volume relations are illustrated for a normal dog (dotted-line loop on the left), a dog with advanced mitral regurgitation (dashed-line loop in the middle), and a dog with end-stage mitral regurgitation and myocardial failure due to chronic volume overload (solid-line loop to the right). Dogs with mitral regurgitation are able to eject a very large stroke volume while maintaining normal or nearly normal contractility for long periods of time. In this circumstance, ejection fraction is markedly increased, and end-systolic volume and contractility are essentially normal. The slope (E_{max}) of the line connecting the end-systolic wall stress-volume end-points from each loop and the x intercept (V_o) define myocardial contractility. Myocardial failure eventually develops, as indicated by the reduced ("flattening") slope (E_{max}), rightward shift of V_o, increased end-systolic volume, and declining ejection fraction.

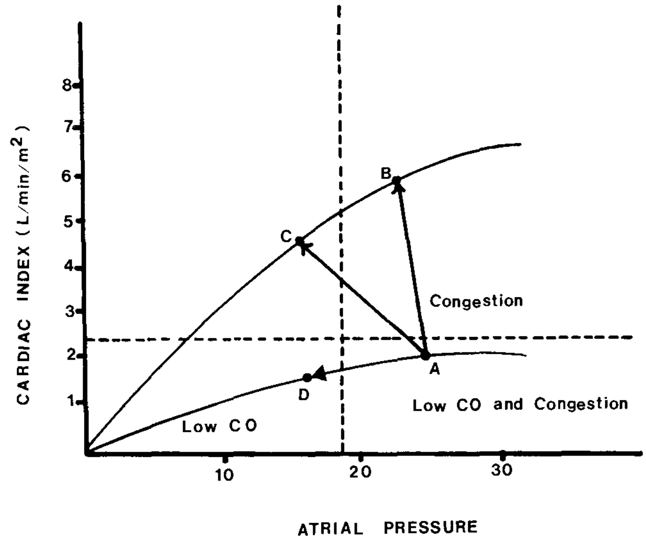


FIGURE 12–5

A Frank-Starling curve of a patient in class IV heart failure (point *A*). With myocardial failure, administration of a positive inotrope or arteriolar dilator causes improvement to point *B*; with a positive inotrope and diuretic (or venodilator) or balanced vasodilator, improvement occurs to point *C*. Patients with mitral regurgitation can move from point *A* to point *C* with an arteriolar dilator or a balanced vasodilator. Overzealous diuretic administration or dehydration can result in the patient's cardiovascular function moving to point *D*. Notice that this causes little change in cardiac index. (From Kittleson M. Concepts and therapeutic strategies in the management of heart failure. *In* Kirk RW [ed]: Current Veterinary Therapy. Vol VIII. Philadelphia, WB Saunders, 1983, p 279.)

from the ventricle (regurgitant volume), and the diastolic pressure of the LV.[29] Pulmonary edema can develop when the regurgitant volume is relatively modest if the atrium is small and noncompliant. An enlarged, compliant LA can accommodate a fairly large volume of mitral regurgitation with a relatively modest rise in pressure. Thus, congestive signs may not correlate with the degree of regurgitation or left atrial size.

The regurgitant volume is a function of the pressure gradient between the LA and LV and the size of the regurgitant orifice.[30] The size of the regurgitant orifice is a dynamic quantity that changes as the ventricle contracts. Arterial vasodilating drugs reduce the volume of mitral regurgitation by two mechanisms: (1) they reduce the LV-LA pressure gradient, and (2) they cause the ventricle (and the mitral annulus) to contract at a faster velocity, thereby reducing regurgitant orifice size.[30] The vasodilating effect of ACE inhibition is more modest and dependent on the degree of neurohormonal activation. Direct-acting arterial vasodilators, although more potent, have the disadvantage of evoking reflex tachycardia.

Diuretics and venodilators diminish plasma volume and increase venous capacitance, respectively, thereby directly reducing left atrial pressure. Diuretics effectively relieve congestive signs in dogs with DCM or MR. For this reason, diuretics are an essential component of therapy. Their use evokes marked neurohormonal responses, which may be disadvantageous. To the extent they reduce left ventricular size, diuretics and venodilators reduce mitral regurgitant volume. Positive inotropic drugs increase the velocity of myocardial contraction, thereby reducing regurgitant orifice area and regurgitant volume.[31] This effect may not be very important for weak positive inotropes like digoxin. More potent positive inotropic drugs, such as milrinone and dobutamine, are more likely to induce a substantial reduction in regurgitant volume.

SHUNTING DEFECTS. Ventricular septal defects (VSD) cause hemodynamic alterations similar to those observed in mitral regurgitation. Because the shunted blood is ejected from the left ventricle into a low-pressure reservoir (the right ventricle), the increase in wall stress and oxygen consumption is minimal. As in dogs with mitral regurgitation, myocardial function is relatively well preserved for a variable period of time, depending on the size of the defect. Arterial vasodilators decrease the LV-RV pressure gradient, thereby reducing the shunt fraction, slowing the progression of cardiac enlargement, and delaying the onset of heart failure.[32] In patients with a VSD, the size of the hole in the septum is fixed. Positive inotropic drugs do not effect any change in the volume of shunted blood.

In other types of volume overload, such as PDA or aortic regurgitation, the LV must eject its entire stroke volume into the high-pressure aorta. Wall stress, myocardial work, and oxygen consumption are concomitantly higher, resulting in earlier development of myocardial failure.[33] In these circumstances, medical management consists of afterload reduction with arterial vasodilators or ACE inhibitors, diuretics to alleviate signs of congestion, and positive inotropic drugs to improve failing contractility. Surgical repair should be accomplished before irreversible myocardial failure ensues. This is routinely accomplished in dogs with a PDA.

Chronic Pressure Overload

Acute, experimentally created aortic stenosis results in increased intraventricular pressure, causing wall tension or stress during systole (afterload) to increase. This increased afterload initially results in an increase in end-systolic volume and a decrease in stroke volume. The myocardium responds to this pressure overload through concentric hypertrophy, wherein the sarcomeres replicate in parallel, causing the muscle fibers to thicken.[18] Concentric hypertrophy returns systolic wall stress and end-systolic volume back to normal. However, capillary density and myocardial perfusion do not increase in proportion to the increase in muscle mass.[34] Chronic myocardial hypoxia results in premature death of myocardial cells. Myocardial failure occurs in dogs with pulmonic stenosis and in some dogs with congenital subaortic stenosis as global myocardial function progressively declines.[35] The most common sequela of severe subvalvular aortic stenosis in dogs is sudden death from ventricular arrhythmia, presumably as a result of myocardial hypoxia.[35] Severe concentric hypertrophy and ischemia-induced myocardial fibrosis substantially compromise left ventricular compliance and can cause diastolic dysfunction.

Successful treatment of left- or right-sided heart outflow obstruction is best accomplished by relieving the obstruction, either by surgery or balloon valvuloplasty.[36, 37] In those patients with signs of heart failure, treatment with digoxin can provide modest improvement, but congestive signs are best treated with exercise restriction, diuretics, and venodilators. Control of heart rate is important in patients with suspected compliance failure (severe hypertrophy or extensive myocardial fibrosis). The efficacy of ACE-inhibiting drugs has not been evaluated in dogs with outflow tract obstructions, but such therapy looks promising in experimentally created obstructions.[38] Arterial vasodilating drugs should be avoided in patients with severe outflow tract obstructions as they are likely to precipitate serious systemic hypotension and reflex tachycardia, thereby further diminishing myocardial perfusion.

RIGHT- VERSUS LEFT-SIDED HEART FAILURE

In animals with heart failure, congestion develops as a consequence of excessive venous pressure due to the

combined effects of increased plasma volume (sodium and water retention) and decreased venous capacitance (venoconstriction). With left-sided heart impairment, pulmonary venous pressures increase, resulting in pulmonary edema and signs of respiratory distress (i.e., left-sided CHF). With right-sided heart impairment, systemic venous pressures rise, resulting in hepatomegaly and ascites (i.e., right-sided CHF). Because the capacitance of the splanchnic veins and the systemic venous reservoir is large, a rather substantial increase in blood volume is required to raise systemic venous pressure. As a result, right-sided congestive signs tend to develop slowly.[39]

By comparison, the capacitance of the pulmonary veins is small. Relatively small changes in blood volume or its distribution can cause a rapid rise in pulmonary venous pressure and pulmonary edema. Sudden increases in sympathetic tone (fear, anxiety, exercise) constrict the splanchnic veins, causing a shift of the circulating blood volume from the systemic to the pulmonary venous reservoir. This is one reason for the often rapid onset of pulmonary edema in animals with left-sided heart failure.

TREATMENT STRATEGIES

ACUTE CONGESTIVE HEART FAILURE

Acute heart failure can develop suddenly with the onset of a new and rapidly progressing disease or from exacerbation of a previously existing chronic disorder. Most affected dogs and cats suffer from a chronic, pre-existing cardiac disorder. Some owners discontinue previously prescribed diuretics, particularly when their pet begins to urinate excessively. A new arrhythmia, such as atrial fibrillation, can also precipitate signs of acute heart failure in a previously compensated patient. Dietary changes or other environmental stresses occasionally precipitate heart failure. Identification of the underlying precipitating event helps guide therapy. Dogs with dilated cardiomyopathy are often presented with fulminating pulmonary edema due to acute decompensated left-sided heart failure and profound myocardial failure. There is often no prior history of heart disease and no identifiable precipitating event. A number of drugs and therapies can be useful for treating acute CHF.

TREATMENT PRIORITIES

Pulmonary Edema Associated with Mitral Regurgitation or Dilated Cardiomyopathy

In patients with acute, decompensated CHF, immediate priorities include

1. Relief of life-threatening pulmonary edema,
2. Maintenance of adequate systemic arterial blood pressure, and
3. Adequate delivery of blood flow to vital tissues.

One should select drugs with a rapid onset of action and proven hemodynamic benefits. Many drugs capable of improving exercise capacity or prolonging survival in patients with chronic heart failure are neither appropriate nor effective when administered to acutely decompensated patients. Conversely, many of the drugs used to optimize a patient's prospects for short-term survival are not effective for increasing exercise capacity or prolonging survival when they are administered chronically. Treatment designed to realize long-term therapeutic goals should be implemented *after* the acutely ill patient is stabilized.

OXYGEN SUPPLEMENTATION. Arterial hypoxemia can be best remedied by providing an oxygen-enriched environment and by rapidly reducing left atrial and pulmonary venous pressure. Oxygen cages provide oxygen concentrations (FIO_2) in the range of 40 to 50 percent. Alternatively, oxygen can be administered via an intranasal catheter, providing oxygen concentrations as high as 90 percent, depending on the flow rate used.[40]

INTRAVENOUS DIURETICS AND VASODILATORS. Acute reduction of pulmonary venous pressure (and pulmonary edema) is achieved by IV administration of a potent vasodilator to redistribute intravascular fluid volume and IV administration of a potent diuretic to reduce total blood volume. Furosemide is a potent loop diuretic that should be administered IV when severe cardiogenic pulmonary edema is present. Large doses (2.2 to 4.4 mg/kg in dogs, 1.1 to 2.2 mg/kg in cats) may be administered frequently (initially every 1 to 2 hours) until respiratory rate and dyspnea start to decline. Dosage should then be reduced (2 to 4 mg/kg q 8 to 12 hr in dogs, 1 to 2 mg/kg q 8 to 12 hr in cats). Excessive dosing can lead to dehydration, electrolyte depletion, renal failure, low cardiac output, and circulatory collapse. Appropriate monitoring requires periodic determination of serum electrolytes and urine production.

Sodium nitroprusside is an extremely potent, direct-acting, mixed vasodilator that is primarily used to rescue dogs with life-threatening pulmonary edema caused by mitral regurgitation or dilated cardiomyopathy.[41] In this circumstance, it may be more effective than furosemide for immediately decreasing left ventricular filling pressure, left atrial pressure, and pulmonary venous pressure. Its hemodynamic effects when used in animals with CHF include decreased right atrial and pulmonary capillary wedge pressures, decreased systemic vascular resistance, and increased cardiac output.[41] In dogs with mitral regurgitation, regur-

gitant volume can be markedly reduced as the LV-LA pressure gradient and area of the regurgitant orifice are diminished.[30]

Following dilution in 5 percent dextrose, sodium nitroprusside is infused using a constant rate infusion pump (initial rate, 1.0 μg/kg/min). The rate of administration is titrated to effect by monitoring blood pressure (and ideally, pulmonary capillary wedge pressure), to a maximum dose of 10 μg/kg/min. In most cases, an infusion rate of 2.0 to 5.0 μg/kg/min suffices. Adverse side effects include hypotension, tachycardia, nausea, vomiting, and, with chronic administration, cyanide poisoning. Because of its short half-life, the serious consequences of profound hypotension are avoidable when patients are carefully monitored. Hypotension is usually managed by slowing the rate of infusion.

Alternatively, hydralazine tablets (crushed and mixed with water) can be administered (0.5 to 2.0 mg/kg PO) in combination with a nitrate (either nitroglycerin ointment, 1/4 to 3/4 inch cutaneously to the pinna q 8 to 12 hr, or isosorbide dinitrate, 0.5 to 2.0 mg/kg q 8 hr PO). This latter approach seems to work better in dogs with mitral regurgitation than with dilated cardiomyopathy.

POSITIVE INOTROPES. Inotropic support is very important with acute heart failure due to dilated cardiomyopathy, and it is also used to treat severely decompensated mitral regurgitation. Dobutamine and dopamine are synthetic catecholamines that are more efficacious than digoxin for acute management of profound myocardial failure. Because of their very short half-lives, they are best suited to short-term IV use. Efficacy is limited during chronic administration by down regulation of β-adrenergic receptors.[42] Therefore, these drugs are generally used only for 24 to 72 hours.

Dobutamine increases contractility with little change in heart rate or afterload. For this reason, it is preferred over other sympathomimetic drugs for the treatment of heart failure. Dobutamine hydrochloride is administered by constant IV infusion (5.0 to 15.0 μg/kg/min). In patients with CHF, the volume of the infusion should be minimized. With the recent availability of generic drug supplies, treatment with dobutamine is now more affordable and practical in veterinary patients.

Dopamine stimulates β_1-receptors and, at high doses, also releases norepinephrine from sympathetic nerve terminals. At low doses (< 5.0 μg/kg/min), dopamine causes selective arteriolar dilation in renal, mesenteric, coronary, and cerebral vascular beds.[43] For this reason, it may be useful for treating patients with concurrent heart and renal failure. At high doses, dopamine causes generalized systemic arteriolar vasoconstriction, an undesirable effect with heart failure. Dopamine hydrochloride is administered by continuous IV infusion at 2 to 8 μg/kg/min.

The most common adverse effects observed with dobutamine or dopamine are tachycardia and arrhythmia. These effects are usually dose related and can be remedied by stopping or slowing the administration rate.

Amrinone and *milrinone* are cardioactive bipyridines that increase myocyte concentrations of cyclic adenosine monophosphate (AMP) by phosphodiesterase inhibition. These potent positive inotropes also have direct-acting arterial vasodilator properties.[44] Amrinone and milrinone are currently available only as IV preparations for short-term use in patients with decompensated heart failure. Neither has been used extensively in client-owned animals. In dogs, amrinone can be initially administered as a slow IV bolus (1.0 to 3.0 mg/kg), and thereafter by constant IV infusion (10 to 100 μg/kg/min). Milrinone is 10 to 30 times more potent than amrinone, but the dose of the IV preparation is not well established.

Commonly observed adverse effects of the bipyridines include a dose-related increase in heart rate; gastrointestinal signs, including diarrhea and anorexia; and at high doses, hypotension. Amrinone and milrinone also can induce or potentiate serious ventricular arrhythmia.

Digoxin is a comparatively weak positive inotrope with a narrow margin of safety. In most cases, digitalis glycosides can be administered orally, starting at maintenance dosage (dogs: 0.22 mg/m^2, or 0.005 to 0.008 mg/kg q 12 hr [subtract 10 percent if elixir is used]; cats: 2 to 3 kg, 0.0312 mg q 48 hr PO; 4 to 5 kg, 0.0312 mg q 24 to 48 hr; > 6 kg, 0.0312 mg q 24 hr). Rapid intravenous digitalization is rarely necessary in dogs with acute heart failure except to control certain supraventricular tachyarrhythmias.

Treatment of Serious Arrhythmias

The most commonly encountered arrhythmias in dogs with acute heart failure are atrial fibrillation, atrial tachycardia, and ventricular tachycardia.[13, 45] Substantial hemodynamic and clinical improvement can often be realized by successful treatment (chapter 18). Rapid oral digitalization is appropriate in dogs with atrial fibrillation and a rapid ventricular response and in those with paroxysmal or sustained atrial tachycardia. One practical method to hasten the achievement of therapeutic blood concentrations is simply to give the calculated maintenance dose three times rather than twice daily, for 1 or 2 days. The IV route is reserved for use in dogs with atrial fibrillation or sustained atrial tachycardia, an excessively fast heart rate (usually greater than 220 beats/minute), and life-threatening hemodynamic compromise. Intravenous

diltiazem may be a safer and more effective treatment in this situation.

Immediately life-threatening ventricular tachycardia is most appropriately managed by the administration of IV lidocaine or procainamide (chapter 18). If hypoxemia precipitated the arrhythmia, oxygen supplementation and relief of pulmonary edema are essential. Acid-base and electrolyte disturbances should also be treated appropriately. If digitalis toxicity is a likely cause, the slow infusion of potassium salts or phenytoin may effectively abort the arrhythmia.

Low-Output Heart Failure

Clinical signs referable to low cardiac output and hypotension may accompany acute heart failure associated with acute cardiac tamponade, massive pulmonary thromboembolism, or sudden myocardial depression due to anesthetic or circulating toxins. Congestive signs and edema are usually absent initially because renal and neurohormonal compensatory responses that act to conserve sodium and water have not had a chance to operate. Low-output heart failure is best treated by resolving the precipitating event, by optimizing preload, and by providing inotropic support.

Acute Heart Failure in Feline Cardiomyopathy

Cats with acute pulmonary edema due to hypertrophic or restrictive cardiomyopathy require prompt, aggressive treatment. Because these animals have heart failure due to diastolic dysfunction, they do not benefit from positive inotropic drugs and may be made worse if arterial vasodilators are used. Therapy should be designed to relieve congestion and improve ventricular filling. Most affected cats respond initially to IV furosemide (2 to 4 mg/kg) combined with cutaneous 2 percent nitroglycerin ointment (1/8 to 1/4 inch applied to the pinna q 8 hr) and supplemental oxygen therapy. After 24 to 48 hours, edema is usually reduced or resolved, and furosemide dosage should be reduced. Additional drugs can then be administered to prevent thromboembolism, reduce heart rate, and improve diastolic filling. Calcium channel blockers and β-adrenergic receptor blockers have been advocated to improve LV filling and cardiac performance in cats with hypertrophic cardiomyopathy.[7–9] Beta-blockers (propranolol or atenolol) are generally more effective than diltiazem in reducing heart rate. Some cats with chronic HCM or RCM present with acute respiratory distress caused by the accumulation of a large pleural effusion. Successful treatment requires drainage of the pleural space. Thereafter, treatment is based according to the dictates of the underlying disorder.

CHRONIC CONGESTIVE HEART FAILURE

CLINICAL CLASSIFICATION

Human heart failure patients are often categorized into heart failure classes that are based upon exercise ability and severity of clinical signs.[46] This New York Heart Association scheme has been modified for veterinary use as follows: *Functional class I* represents heart disease without exercise intolerance or signs of heart failure. Cardiomegaly is mild or absent. *Functional class II* denotes animals that exhibit cardiac-related exercise intolerance, however mild. These animals do not generally display radiographic evidence of pulmonary edema, but substantial cardiomegaly is usually apparent. Patients with diastolic dysfunction due to left ventricular hypertrophy may exhibit minimal radiographic evidence of left ventricular enlargement. *Functional class III* includes animals with signs of heart failure during normal activity. In animals with left-sided heart failure, radiographic changes include marked cardiomegaly or at least left atrial enlargement, distended pulmonary veins, perihilar congestion (dogs but not cats), and interstitial or alveolar infiltrates. In those patients with right-sided heart failure, the liver may be enlarged, ascites is usually modest or absent, pericardial and/or pleural effusion is present, and right-sided or generalized cardiomegaly is evident. *Functional class IV* animals are in severe heart failure and display obvious clinical signs at rest or with minimal activity. Radiographs demonstrate pulmonary edema with left-sided heart failure, ascites or hydrothorax with right-sided heart or biventricular heart failure, and cardiomegaly.

Limitations of Heart Failure Classification Schemes

This classification scheme has obvious limitations. Exercise tolerance in dogs and cats is rarely determined by any objective measure, and mild exercise limitations often go unnoticed. Thus, the distinction between class I and class II patients is often pragmatically based on radiographic heart size and cardiac function as judged by thoracic radiographs and/or an echocardiogram. Class III and class IV patients represent advanced disease and are more easily identified. In addition to these difficulties, the optimal point in time (Fig. 12–7) when one or more cardiac drugs should be administered to prevent disease progression is largely unknown.

DILATED CARDIOMYOPATHY AND MITRAL REGURGITATION

Treatment of class I and class II patients with DCM or mitral regurgitation is controversial. In humans with

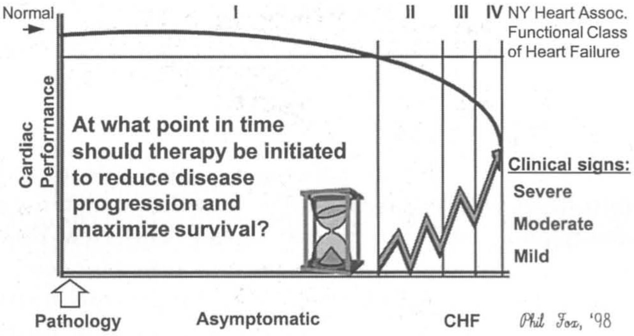


FIGURE 12–7

The optimal timing for initiating medical therapy in dogs or cats with progressive cardiovascular disease is uncertain and remains the focus of much debate. Compensatory neurohormonal responses are activated at different times and to varying degrees. This varies not only between types of heart disease but also within a particular disorder, depending upon the severity of its structural and functional derangements. Clinical studies will be required to clarify the best sequence or combination of drugs to combat the deleterious consequences of neurohormonal activation in heart failure. (Courtesy of Dr. Philip Fox, The Animal Medical Center.)

class I asymptomatic left ventricular dysfunction due to ischemia or DCM, treatment with ACE inhibitors delayed the onset of CHF but did not prolong survival.[23] One report suggests that the same result might be achieved in asymptomatic dogs with dilated cardiomyopathy,[47] although this requires more extensive clinical evaluation.

Treatment of class II patients with systolic dysfunction generally includes discontinuation of strenuous activities or exercise and, potentially, an ACE inhibitor and digoxin (Fig. 12–8). Mild sodium restriction is sometimes advocated, but there is no evidence that it retards onset of heart failure, improves longevity, or is harmful. Currently, no drugs have been shown to alter the natural course of heart disease or prolong survival in class II patients.

Single-agent therapy with diuretics is usually not advocated since these drugs activate neuroendocrine responses that might hasten the progression of heart failure.[48] It is not known to what effect this is clinically important. Proponents of monotherapy with an ACE inhibitor claim that it delays the onset and retards the progression of heart failure by virtue of its ability to prevent sodium and water retention, moderate vasoconstriction, and modify the adverse consequences of tissue remodeling.[23, 49] Others have questioned the efficacy of this approach, particularly in dogs with mitral regurgitation. Studies in Cavalier King Charles spaniels with mitral regurgitation suggest that activation of the renin-angiotensin system is not measurable, at least by plasma assays, until congestive signs are apparent (classes III and IV).[50] More definitive recommendations require further clinical study.

An alternative regimen for class II patients is to use modest doses of diuretics (furosemide at 0.5 to 1.0 mg/kg/day), digoxin (dosed to achieve a serum concentration of about 1.0 to 1.5 ng/dl), in combination with ACE inhibitors (enalapril or lisinopril at 0.5 mg/kg q 12 to 24 hr PO). This *balanced* pharmacologic approach is designed to improve clinical signs and to mitigate against the adverse consequences of neurohormonal activation. It has been argued that digoxin is unnecessary in dogs with endocardiosis that have no or only mild myocardial dysfunction, and that its use enjoins an unacceptable risk of adverse drug effects. Proponents of digitalis cite the importance of its effects on the autonomic nervous system, as well as its positive inotropic action.[19, 51] To date, there are no clinical trials in dogs or cats to indicate optimal therapies.

Patients in functional class III have signs of heart failure during normal activity. Diuretics, ACE inhibitors, digoxin, salt-restricted diets, and curtailment of physical activity are often advised. Diuretics are administered more frequently and at higher doses (furosemide, 1 to 2 mg/kg q 12 hr PO) than in class II patients. ACE inhibitors (enalapril or lisinopril, 0.5 mg/kg q 12 hr PO) are particularly beneficial for improving exercise capacity and delaying the onset of refractory heart failure.[52] They decrease the concentration of plasma angiotensin II, a potent vasoconstrictor,

EARLY, CLASS I & II HEART FAILURE	ACE inhibitor	+/-	Furosemide (low dose)	+/-	Digoxin
MODERATE, CLASS III HEART FAILURE	ACE inhibitor	+	Furosemide (moderate dose)	+	Digoxin
SEVERE, CLASS IV HEART FAILURE	ACE inhibitor + nitrate + amlodipine or hydralazine	+ + +	Furosemide (high dose) thiazide spironolactone	+	Digoxin
REFRACTORY HEART FAILURE	*Intensive Pharmacotherapy* IV furosemide and/or diuretic combinations IV nitroprusside + dobutamine, dopamine IV amrinone or milrinone				

FIGURE 12–8

Treatment strategies for heart failure caused by systolic pump (myocardial) failure. In general, therapy escalates in proportion to the severity of clinical signs, as do the risks of adverse drug reactions and interactions. The benefits of using angiotensin-converting enzyme (ACE) inhibitors in all stages of heart failure are well established in dogs with dilated cardiomyopathy. Their efficacy in dogs with mitral regurgitation is less clear, particularly in class I and class II heart failure. The indication for digoxin is also controversial for treating dogs with early mitral regurgitation. Some clinicians advocate its use early in the course of heart failure, beginning in class I or II and continuing through class IV; others recommend digoxin only in the latter stages of heart failure (classes III and IV). High doses of furosemide, combinations of diuretics, and concurrent administration of vasodilators and ACE inhibitors are reserved for dogs in class IV heart failure.

which reduces systemic vascular resistance. This leads to increased forward blood flow. In dogs with mitral regurgitation, the left ventricle can then eject more blood into the aorta, thereby reducing the volume of blood regurgitated into the left atrium. In addition, plasma aldosterone is reduced, which leads to decreased renal sodium and water retention. Digoxin is used in virtually all dogs with DCM, but there is less unanimity of opinion regarding the use of digoxin in dogs with mitral regurgitation at this stage.

The same drugs used in class III patients are also used in class IV patients, but the doses used are usually titrated upward. Chronic therapy of class IV patients often requires a variety of drug combinations tailored to meet the needs of the individual patient. Such aggressive therapy engenders the unavoidable possibility of adverse drug reactions and often unexpected drug interactions. Digoxin is advised in class IV patients if it has not already been prescribed. High doses of furosemide (2 to 4 mg/kg q 8 to 12 hr) or combinations of diuretics are often used to treat refractory edema. Addition of a different class of diuretic blocks the adaptive responses that limit single-agent therapy, resulting in a synergistic effect.[53] We sometimes combine either chlorothiazide or hydrochlorothiazide with furosemide to combat refractory edema. Daily treatment with furosemide and a thiazide diuretic often causes dehydration and electrolyte depletion, particularly in cats. Administration of a thiazide drug every 2 or 3 days (in addition to furosemide) often resolves refractory pulmonary congestion without causing dehydration. Hypokalemia is uncommon in dogs but frequently occurs in anorectic cats receiving diuretics. It can be prevented or minimized by oral potassium supplementation or, theoretically, by adding spironolactone (1.0 to 2.0 mg/kg q 12 hr PO) to the treatment regimen.

An arterial vasodilator and/or a nitrate can be added to conventional therapy in dogs with pulmonary edema that is refractory to treatment with furosemide, an ACE inhibitor, and digoxin. A conservative approach is to add a nitrate first. Other more potent vasodilators can be added subsequently, if necessary. Nitroglycerin ointment can be applied cutaneously, but the dose and efficacy of this modality are uncertain. Two other nitrates, isosorbide dinitrate and its major metabolite isosorbide mononitrate, are available for oral therapy. Safe and effective dosages of these two drugs have not been determined in dogs or cats by controlled clinical trials. Therefore, it is advisable to start low and titrate upward to effect (see section on pharmacology of nitrates). A dosage-free interval, typically 10 to 12 hours long, is advised when using nitrates to avoid the phenomenon of tolerance.

Some patients with systolic (myocardial) failure improve with more aggressive afterload reduction. In dogs with mitral regurgitation, hydralazine increases forward stroke volume and decreases regurgitant flow, resulting in a decrease in left atrial pressure and reduction in pulmonary edema.[54] Hydralazine also improves renal clearance and increases the effectiveness of furosemide.[55]

Another vasodilator, amlodipine, can be used for the same purpose as hydralazine.[56, 57] Amlodipine blocks the calcium channels in vascular smooth muscle to effect arterial vasodilation. It has reduced symptoms and improved exercise tolerance in humans with CHF without increasing cardiovascular morbidity or mortality. In fact, amlodipine prolongs survival of human patients with dilated cardiomyopathy.[57] The efficacy of this compound in dogs with dilated cardiomyopathy or chronic degenerative valve disease has not been determined. Preliminary clinical observations suggest that amlodipine is efficacious in dogs with heart failure complicated by systemic hypertension and in normotensive dogs with refractory heart failure due to mitral regurgitation. Its 30-hour half-life allows once-daily dosing, but, concomitantly, its peak effect is not realized for 4 to 7 days.[58] This long half-life of amlodipine is disadvantageous should adverse effects, such as hypotension, occur.

The concomitant administration of an ACE inhibitor and arterial vasodilator must be approached cautiously since hypotension severe enough to produce severe weakness, renal failure, and death can result. Arterial vasodilators, especially hydralazine, can cause reflex tachycardia, necessitating use of a negative chronotropic agent. A digitalis glycoside is generally the first choice for this purpose; a β-adrenergic receptor blocking agent, such as propranolol, is the second choice, but many of these agents decrease contractility.

TRICUSPID REGURGITATION

Tricuspid regurgitation (TR) results in a volume overload of the right-sided heart in the same fashion that mitral regurgitation causes volume overload of the left-sided heart. The function of the right ventricular myocardium in TR is unknown; it may be normal or depressed. Tricuspid regurgitation resulting from chronic acquired valve disease (endocardiosis) occurs mainly in dogs with concurrent mitral regurgitation, but it sometimes appears as an isolated problem. It is important to ascertain whether pulmonary hypertension is present, as it can greatly augment the volume of regurgitant flow. Therapy of right-sided heart failure due to TR generally includes diuretics, an ACE inhibitor, and digitalis. Orally administered drugs may be poorly absorbed, and doses may have to be adjusted accordingly. In some cases, parenteral administration of furosemide is needed for initial stabilization. Repeated abdominocentesis is often required when ascites is refractory to drug therapy.

Tricuspid regurgitation can also develop as a conse-

quence of pulmonary hypertension and right-sided heart dilatation. Successful treatment of pulmonary hypertension reduces tricuspid regurgitant flow and lowers right atrial pressure. This outcome can sometimes be accomplished in dogs with heartworms but is otherwise difficult. High doses of calcium channel blockers are effective in some human patients with idiopathic pulmonary hypertension.[59] When congenital tricuspid dysplasia occurs as an isolated lesion, it is treated medically as described earlier. When tricuspid dysplasia occurs together with pulmonic stenosis, treatment of pulmonic stenosis (balloon valvuloplasty or surgery) will lower right ventricular systolic pressure, thereby decreasing regurgitant flow. Surgical repair or replacement of the tricuspid valve can also be considered.

PATENT DUCTUS ARTERIOSUS

Definitive treatment of dogs with a PDA can be accomplished either by surgical ductal ligation or by transcatheter ductal occlusion using coils or other devices (see Fig. 24–46) (chapters 24, 39).[60, 61] Dogs with congestive heart failure and myocardial failure are treated in the same way as dogs with DCM, except that the PDA should be occluded as soon as the animal is stabilized. An IV positive inotrope, such as dobutamine, should be administered during surgery and in the early postoperative period in these cases to offset the myocardial depressant effects of anesthesia.

AORTIC INSUFFICIENCY

Aortic regurgitation is most commonly caused by bacterial endocarditis (chapter 26). Signs of heart failure often develop suddenly, and rapid progression is the rule.[62] Acute therapy consists of diuretic administration in combination with an ACE inhibitor or vasodilators. Chronic therapy consists of digoxin, diuretics, ACE inhibitors, and/or vasodilators (usually hydralazine). Prognosis is poor. Most dogs that are severely affected die within weeks of diagnosis.

PULMONIC STENOSIS

Right-sided heart failure is a common sequela to severe pulmonic stenosis. Medical treatment consists of exercise restriction, sodium restriction, digoxin, and, most importantly, diuretics (the value of ACE inhibitors is unknown). Relief of the obstruction offers the best chance of long-term survival. Balloon valvuloplasty is the preferred treatment for those lesions amenable to this approach (chapter 9); surgical repair is also an option (chapter 39). Some dogs develop a dynamic muscular outflow tract obstruction following repair of the stenotic valve. Treatment with a β-adrenergic blocker or calcium channel blocking drugs can be used to abolish or reduce the obstruction.

AORTIC STENOSIS

Left-sided heart failure is uncommon in dogs with valvular or subvalvular aortic stenosis (SAS) unless there is concurrent mitral valve dysplasia. This combination of defects is particularly difficult to treat, and the outcome is usually unsatisfactory. Occasionally, dogs with isolated (subvalvular) aortic stenosis develop congestive heart failure.[35] Contractile indices are usually reduced, but diastolic compliance failure may also play a role. The left ventricle is usually extensively hypertrophied, and there is a substantial amount of myocardial fibrosis. Exercise seems to worsen congestive signs, and sudden death is a common sequela. Conservative doses of furosemide are necessary to control edema when present, since the hypertrophied left ventricle is dependent on moderately elevated filling pressures to ensure optimal loading and stroke volume. Digoxin provides inotropic support and may improve diastolic filling by reducing heart rate. The value of ACE inhibition is unknown. Direct-acting arterial vasodilators can precipitate severe hypotension and should be avoided.

SYSTEMIC HYPERTENSION

It is uncommon for systemic hypertension to produce signs of left-sided heart failure. While LV hypertrophy is commonly documented using echocardiography in hypertensive dogs and cats, the left atrium is not generally enlarged. More often, heart failure results when systemic hypertension complicates some pre-existing condition, such as mitral regurgitation. The most common disease associated with systemic hypertension in dogs is renal disease or hyperadrenocorticism; in cats, renal disease or hyperthyroidism is usually causative (chapter 35).

When systemic hypertension is associated with CHF, it is treated aggressively using diuretics, vasodilators, ACE inhibitors, β-adrenergic blockers, and calcium channel blocking agents. Calcium channel antagonists and β-blockers must be used cautiously if myocardial failure is present. We currently favor amlodipine for treating systemic hypertension. For cats weighing less than 5.0 kg, the dose is 0.625 mg sid PO[63] (may be titrated to 2.5 mg bid if necessary); for cats over 5.0 kg, 1.25 mg sid is used initially. The best dose of amlodipine for dogs is uncertain,[64] but it may be initiated at 0.05 to 0.10 mg/kg sid to bid PO. The dose is titrated to effect, up to 2.0 mg/kg sid, recognizing that the plateau concentration is not achieved until 5 to 7 days after commencing therapy. Refractory cases may respond to combined treatment with amlodipine and atenolol.

REFRACTORY CHRONIC HEART FAILURE

Most animals with chronic heart failure suffer from a degenerative or heritable disease for which there is no known cure. However, some have an identifiable systemic disorder that precipitates decompensated heart failure (e.g., systemic hypertension, systemic inflammation, neoplasia, hypothyroidism, anemia, pneumonia, hyperadrenocorticism, pulmonary thromboembolism, and renal failure) (chapter 33). Congestive heart failure may be alleviated when these complicating disorders are identified and treated. Therefore, it is always advisable to measure blood pressure, obtain current radiographs and an electrocardiogram (ECG), and obtain a complete clinical pathology data base. The precise cause of worsening heart failure is often difficult to identify. Echocardiography is desirable in all cats and dogs with refractory heart failure. Other specialized diagnostic procedures, including ambulatory ECG recordings and invasive measurement of intracardiac or vascular pressures, are sometimes required to guide therapy. The inherent risks and complications of treatment are always greatest in animals with refractory heart failure. Referral to a specialist should be sought before embarking on an unfamiliar or unconventional treatment protocol.

DRUGS USED IN TREATING HEART FAILURE

POSITIVE INOTROPIC AGENTS

A number of agents are available to treat myocardial failure. Table 12–2 summarizes the clinically important properties of the commonly used positive inotropic drugs.

DIGITALIS GLYCOSIDES

Since their auspicious beginning in the treatment of dropsy by William Withering[65] in 1785, the digitalis glycosides have been embroiled in controversy regarding their use, mechanism of action, and efficacy. They have become the most studied of all cardiac drugs, with reports documenting efficacy[66–68] or lack of efficacy[69–73] in the treatment of heart failure. In a landmark double-blind, placebo-controlled study of 6800 humans with heart failure and reduced ejection fraction, digoxin reduced the rate of overall hospitalization but had no effect on mortality (survival). The latter distinguished it from other, more potent positive inotropes that increase mortality.[74] This study population represented different diseases compared with those that affect dogs and cats. Therefore, direct extrapolation is uncertain.

There is great individual variability in patient responses to digoxin, and it has been difficult to define therapeutic end-points.[29] In one study, only 5 of 22 treated dogs had a measurable increase in contractility, but those 5 lived significantly longer than the dogs that did not respond in this fashion.[75] However, the inability to measure an inotropic response by routine echocardiographic measurements does not preclude a positive inotropic effect or an efficacious clinical response to digoxin.[29, 39, 51] Treatment with digoxin should not be abandoned on this basis, nor should it be universally embraced based on its theoretic benefits. Because some patients respond to its use, digoxin should be tried in most dogs with myocardial failure.

TABLE 12–2
Commonly Used Positive Inotropic Drugs

Group	*Generic Name*	*Brand Name*	*Mechanism of Action*	*Extracardiac Effects*	*Toxicity*	*Dosage Range**
Digitalis Glycosides	Digoxin	Lanoxin Cardoxin	Increased Ca^{++} availability Inhibition of Na^+/K^+ ATPase	Autonomic effects: ↓ sympathetic outflow ↑ parasympathetic tone	Anorexia, nausea, vomiting, diarrhea Neurologic signs Cardiac arrhythmia	0.22 mg/m² q12h (dogs) or 0.005–0.008 mg/kg q12h(dogs) 0.005–0.008 mg/kg q24h (cats)
	Digitoxin	Crystodigin				0.033 mg/kg q8–12h (dogs) Not used in cats
Sympathomimetic Amines	Dobutamine	Dobutrex Generics	Increased Ca^{++} availability Increases cAMP via $beta_1$-receptor stimulation	$Alpha_1$ and $beta_2$ receptor stimulation	Tachycardia Cardiac arrhythmia	5.0–20.0 µg/kg/min (dogs) 2.5–10.0 µg/kg/min (cats)
	Dopamine	Generics		Selective renal vasodilation at low infusion rates Generalized vasoconstriction at high infusion rates	Tachycardia Cardiac arrhythmia Nausea, anorexia Phlebitis	2–5 µg/kg/min
Bipyridine Compounds **Phosphodiesterase (PDE) Inhibitors**	Amrinone	Inocor	Increased Ca^{++} availability Inhibition of type III cAMP phosphodiesterase	Peripheral vasodilation	Cardiac arrhythmia Tachycardia Hypotension	1–3 mg/kg slow IV, then 10.0–100.0 µg/kg/min
	Milrinone	Primacor				50 µg/kg slow IV, then 0.375–0.75 µg/kg/min

*See text for discussion.

If no benefit is realized in the face of adverse side effects, digoxin should be discontinued.

PHARMACODYNAMICS. The digitalis glycosides increase contractility in normal myocardium and may also do so in failing myocardium. Their positive inotropic effect in normal myocardium is about one third that of the sympathomimetics (e.g., dopamine, dobutamine) and bipyridine compounds (e.g., amrinone, milrinone). The effect of digitalis on the Na^+-K^+-ATPase pump located on myocardial cell membranes is thought to account for its positive inotropic effect.[76] Digitalis competitively binds to the site at which K^+ normally attaches. This effectively stops pump activity,[77] which increases the intracellular Na^+ concentration. The cell counters by exchanging intracellular Na^+ for extracellular Ca^{++}. These excess intracellular Ca^{++} ions, which are bound by the sarcoplasmic reticulum during diastole, are subsequently released onto the contractile proteins during systole, causing increased contractility.[78]

The sarcoplasmic reticulum of damaged myocardial cells may be unable to bind as much Ca^{++} during diastole or to release as much Ca^{++} during systole.[79] If all or most myocardial cells are badly damaged, it seems unreasonable to expect digitalis to cause a substantial increase in contractility. Poor contractility and elevated diastolic Ca^{++} concentrations could result. Cells that are overloaded with Ca^{++} may be electrically unstable.[80] If digitalis did increase intracellular Ca^{++} in this situation, further electrical instability and arrhythmia formation could occur.

The digitalis glycosides exert other important effects. A therapeutic digoxin plasma concentration partially restores baroreceptor reflexes, which are blunted in heart failure patients; digitalis glycosides increase parasympathetic nerve activity to the sinus node, atria, and AV node.[19, 81] Digoxin decreases overall sympathetic outflow, and the plasma norepinephrine concentration typically decreases following digitalization.[82] As a result, heart rate usually declines. Digitalis glycosides also produce direct effects that help slow AV nodal conduction and prolong the AV nodal refractory period. They are often used as antiarrhythmic agents, mostly for controlling supraventricular tachyarrhythmia.

PHARMACOKINETICS. The pharmacokinetics of the two most commonly used digitalis glycosides, digoxin and digitoxin, are remarkably different despite their similar molecular structures. Approximately 60 percent of digoxin in tablet form is absorbed after oral administration, whereas about 75 percent of that in the elixir is absorbed. There is very little hepatic metabolism of digoxin, so almost all the drug that is absorbed reaches the serum. Twenty-seven percent of digoxin is bound to albumin in the serum.[83] In dogs, the serum half-life of digoxin varies from 23 to 39 hours.[84, 85] Much interpatient variability exists. Digoxin is mainly excreted in the urine via glomerular filtration and renal secretion. About 15 percent is metabolized in the liver. Renal failure reduces renal clearance, total body clearance, and volume of distribution, resulting in an increased serum digoxin concentration.[86] Digoxin is poorly lipid soluble, whereas digitoxin is lipid soluble.

Drug accumulation occurs until a steady-state serum concentration is reached. It takes one half-life to achieve 50 percent of the steady-state serum concentration, two half-lives to reach 75 percent, three half-lives to reach 87.5 percent, and so forth. Thus, it takes about five half-lives (i.e., 5 to 7 days) for digoxin concentrations to reach steady state. Therapeutic serum digoxin concentrations are between 1.0 and 2.5 ng/ml.[87] The clinical trend has been to target the low end of this range.

The pharmacokinetics of digoxin in the cat are controversial. The half-life is variable, ranging from 25.6 to 50.6 hours in one study (mean, 33.5 hours),[88] and 39.4 to 78.8 hours in another (mean, 57.8 hours).[89] The first study reported that the half-life of digoxin increased dramatically to an average of 72.7 hours after prolonged oral administration. The elixir formulation results in a serum concentration approximately 50 percent higher than that of tablet formulation. Most cats dislike the taste of the alcohol-based elixir, and tablets are better tolerated. When digoxin tablets are administered with food, serum concentrations are reduced by about 50 percent compared with the concentrations without food.[89]

Digitoxin has superior pharmacokinetic properties in the dog compared with digoxin.[90] Because its half-life is only 8 to 12 hours in this species, therapeutic serum concentration can be achieved more rapidly than with digoxin, and serum concentration decreases more quickly if a dog becomes toxic. Ninety-five to one hundred percent of orally administered tincture of digitoxin is absorbed; about 90 percent of the drug is bound to serum protein, so a higher dose of digitoxin is needed relative to digoxin. Digitoxin is excreted by the liver, and it can be used safely in dogs with renal failure without adjusting the dose. In the cat, the half-life of digitoxin exceeds 100 hours.[91]

CLINICAL USES AND EFFICACY. The digitalis glycosides are indicated for the treatment of myocardial failure and certain supraventricular tachyarrhythmias. Myocardial failure is present in all patients with dilated cardiomyopathy; often it develops in dogs with chronic, severe aortic regurgitation or a PDA; and it may or may not be present in dogs with heart failure secondary to mitral regurgitation. Its benefit with mild myocardial dysfunction is unknown. Digitalis is not indicated for hypertrophic cardiomyopathy or pericardial disease.

The digitalis glycosides are moderately effective for treating supraventricular premature depolarizations and supraventricular tachycardia and for controlling the ventricular rate in atrial fibrillation. Heart rate control in dogs with atrial fibrillation often requires the combined use of digoxin and calcium channel blocker or a β-adrenergic receptor blocker (chapter 18). Digitalis should be used cautiously in the face of ventricular tachyarrhythmias, as the proarrhythmic effects of digitalis are always a clinical concern.

DIGOXIN. In small dogs (< 20 kg), twice daily administration of digoxin at 0.005 to 0.008 mg/kg PO generally achieves steady-state serum concentrations of between 1.0 and 2.0 ng/ml. Larger dogs (> 20 kg) require a lower dosage per body weight than smaller dogs. The digoxin dosage can be based on body surface area (0.22 mg/m^2 of body surface area q 12 hr PO).[91] When maintenance doses of digoxin are administered, a therapeutic serum concentration is often achieved within 2 to 4.5 days, depending on the initial dose. In one study of dogs given 0.022 mg/kg of digoxin every 24 hours, the serum concentration was within therapeutic range by the second day.[92] Loading doses designed to achieve therapeutic drug concentrations in a short period of time are occasionally used to treat serious supraventricular arrhythmias. Intravenous digitalization is generally reserved for dogs with severe, acute heart failure and a sustained, life-threatening supraventricular tachycardia. It should be given slowly over at least 15 minutes, to avoid peripheral vasoconstriction and increased afterload.[93] For less urgent situations, a therapeutic serum digoxin concentration can be achieved quickly if the usual maintenance dose is simply administered every 8 hr for 1 or 2 days. If there is acute need for positive inotropic support, dobutamine or amrinone is safer and more efficacious than loading doses of digoxin.

It is often necessary to modify (reduce) the *usual* maintenance dose of digoxin. In one study, the digoxin dose (0.005 to 0.23 mg/kg/day) was plotted against serum concentration in dogs with heart failure, and the correlation coefficient (0.39) was statistically significant but weak (1.0 is a perfect correlation).[95] Thus, the milligram per kilogram of body weight dose is only one of a number of variables to consider when administering digoxin. Digoxin is poorly lipid soluble, so obese dogs require lower doses than thin dogs. Since most of the digitalis absorbed is bound to skeletal muscle, patients with reduced muscle mass (cachexia) should be treated with reduced doses. If digitalis is required in a dog with renal failure, the dose of digoxin is reduced by 50 percent or more and subsequently adjusted based on the serum digoxin concentration. Formulas devised for humans to calculate a reduced digoxin dosage in the face of renal failure are not applicable to dogs.[86, 94] There appears to be no correlation between the degree of azotemia and serum digoxin concentration in the dog.[94]

Older dogs should be dosed very cautiously because many have decreased muscle mass and renal insufficiency. The dose of digoxin (mg/kg of body weight) must be reduced in patients with ascites (10 percent with mild, 20 percent with moderate, and 30 percent with severe ascites) because digoxin does not diffuse or bind with ascitic fluid. The need for dosage adjustments in patients with thyroid dysfunction is controversial. Hypothyroidism may reduce digoxin clearance.[96] Hyperthyroid patients have variable sensitivity to digoxin.

Digoxin is the only recommended digitalis glycoside for felines.[97] Cats tolerate the elixir form of digoxin poorly. Therefore, tablets are generally administered. For cats weighing less than 3 kg, digoxin is given at one fourth of a 0.125-mg tablet every other day; for cats weighing 4 to 5 kg, 1/4 tablet is given every 24 to 48 hr; for cats over 6 kg, 1/4 tablet is given daily.

A number of drug interactions can affect digoxin pharmacokinetics. Quinidine displaces digoxin from skeletal muscle binding sites and reduces its renal clearance, resulting in an increased serum digoxin concentration.[98] Although quinidine also displaces digoxin from myocardial binding sites, the net effect is an increased likelihood of intoxication,[99] and this combination should be avoided. If both drugs must be used together, the digoxin dosage is reduced by 50 percent.[100] A number of other drugs, including verapamil, also increase the serum digoxin concentration.[101] Drugs that alter hepatic microsomal enzymes may affect digoxin pharmacokinetics, since about 15 percent of digoxin is metabolized in the liver.[102] Drugs that induce hepatic microsomal enzymes, such as phenylbutazone and the barbiturates, tend to increase digoxin clearance, whereas drugs that inhibit hepatic enzymes, such as chloramphenicol and tetracycline, should increase the serum digoxin concentration. However, one study indicated that chloramphenicol actually decreases serum digoxin concentration in dogs.[103] Such findings emphasize the desirability of monitoring serum digoxin concentrations 3 to 7 days after commencing therapy and whenever signs of toxicity are observed.

DIGITOXIN. The dose of digitoxin in dogs is 0.033 mg/kg q 8 to 12 hr PO.[90] In general, small dogs should receive the dose every 8 hours and large dogs every 12 hours. The cumulative daily dose in small dogs would be greater than that for large dogs on a per-weight basis but similar on a per-body surface area basis. Digitoxin should not be used in cats as its half-life exceeds 100 hours.[91]

ASSESSING EFFICACY. A complete data base, including BUN, serum creatinine, and electrolytes, should be

evaluated before administering digoxin. Factors that alter the dosage (obesity, cachexia) must be noted. Clear client communication is important to help detect signs of toxicity or improvement during early therapy. A reduction in heart rate, resolution of a supraventricular arrhythmia, and clinical improvement are identifiable therapeutic end-points. In most patients, however, the effects of digoxin are uncertain. Many human patients do not recognize the benefits of digoxin until treatment is later withdrawn and their symptoms worsen.[70, 71] If clinical improvement is not observed, the dosage of digoxin should not be increased until its serum concentration has been measured and found to be subtherapeutic (< 0.8 ng/ml).

Ideally, each patient should have serum digoxin concentration measured 3 to 7 days after initiating therapy. The serum sample should be acquired 6 to 8 hours after the last dose. The therapeutic range for serum digoxin concentration is somewhat controversial but can generally be considered to be between 0.8 and 2.0 ng/ml. A serum concentration greater than 2.5 ng/ml is usually considered toxic, and digoxin administration is discontinued until the serum concentration is less than 2.5 ng/ml. Subsequent digoxin doses should be reduced accordingly.

DIGITALIS TOXICITY. Therapeutic end-points include clinical improvement or attainment of a therapeutic serum concentration. Progressive dosing until signs of toxicity occur or until the P-R interval is prolonged is not justified.[104] The incidence of digoxin toxicity in humans is between 13 and 23 percent while 11 to 36 percent of patients have been identified as underdigitalized.[105] In one canine study, 25 percent of dogs receiving digoxin had a serum concentration in the toxic range, and 24 percent had a subtherapeutic concentration.[95] In the enalapril clinical studies (Freedom of Information Summary #315), 15.3 percent of 222 dogs had serum concentrations greater than 3.0 ng/ml and 9.1 percent had clinical signs consistent with digoxin toxicity.

In our experience, clinically significant digitalis toxicity is uncommon if the drug is used judiciously. It occurs most frequently because of dosage errors in administration, particularly during initial stages of digoxin administration when renal function deteriorates unexpectedly; and when the dose is not reduced in concert with weight loss (cachexia). Problems from digitalis intoxication fall into three general classes: (1) signs of gastrointestinal dysfunction, (2) neurologic signs, and (3) myocardial toxicity. Anorexia and vomiting are probably due to the direct effect of the digitalis molecule on chemoreceptors located in the area postrema in the medulla.[106] Although gastrointestinal signs of toxicity usually occur before signs of myocardial toxicity, this generalization is not always the case, particularly when digoxin is administered IV. Digoxin can also cause depression, disorientation, and delirium.

Myocardial toxicity is the most serious complication of digoxin administration. Toxic doses disrupt the normal cardiac electric activity (chapter 16). Digitalis directly slows conduction and alters the refractory period of myocardial cells, making it easier for re-entrant arrhythmia to develop. Sympathetic nerve activity to the heart can increase when high doses of digoxin are administered, resulting in increased normal automaticity.[107] Digitalis promotes abnormal automaticity in myocardial cells that do not usually depolarize spontaneously.[108] Late afterdepolarizations (attributed to cellular Ca^{++} overload, especially induced in myocardium that has been stretched and exposed to a hypokalemic environment) may be caused by digitalis and result in arrhythmia.

Myocardial toxicity can take the form of almost every known rhythm disturbance. Frequently encountered bradyarrhythmias include second-degree AV block, sinus bradycardia, and sinus arrest. Digitalis can also induce supraventricular premature depolarizations, atrial tachycardia, and junctional arrhythmias. At times it may be difficult or impossible to determine whether an arrhythmia is due to digitalis or to the underlying heart disease. The combination of tachycardia and impaired conduction is highly suggestive of digitalis-induced problems. A ventricular tachyarrhythmia appearing in a dog taking digitalis should generally be regarded as digitalis-induced until proved otherwise.

Massive digitalis overdose can produce hyperkalemia and possibly hyponatremia.[109] This is probably caused by digitalis inhibition of the Na^+-K^+-ATPase pumps throughout the body.

Hypokalemia is an important predisposing cause of digitalis myocardial toxicity. Digitalis and potassium compete for the same binding site on the membrane Na^+-K^+-ATPase pump. Hypokalemia leaves more binding sites available for digitalis binding. In turn, hyperkalemia displaces digitalis from the myocardium. Hypercalcemia and hypernatremia potentiate the positive inotropic and toxic effects of digitalis, whereas hypocalcemia and hyponatremia reduce these effects.

TREATMENT OF DIGITALIS INTOXICATION. Gastrointestinal signs related to overdose are treated by drug withdrawal and correction of fluid and electrolyte abnormalities. Conduction disturbances usually require only digitalis withdrawal, although atropine administration is occasionally needed for severe bradyarrhythmias. Ventricular tachycardia should be treated aggressively with lidocaine (see Fig. 18–26), especially when ventricular tachycardia is present (chapter 18).[110, 111] Lidocaine may be given as an initial bolus (2 to 4 mg/kg IV over 1 to 2 minutes), followed by continuous infusion of 30 to 100 μg/kg/min for arrhythmia control. Cats are more sensitive to the neurotoxic effects of

lidocaine, so dose reduction (0.25 to 1 mg/kg IV administered over 5 minutes) and cautious administration are recommended.

Phenytoin can also be used for the treatment of digitalis-induced arrhythmias in the dog. It has properties similar to those of lidocaine. When given IV, the drug vehicle can produce hypotension and exert a depressant effect on the myocardium.[112] The total IV dose is 10 mg/kg, administered in 2-mg/kg increments over 3 to 5 minutes. Phenytoin can also be administered orally (35 mg/kg q 8 hr).[113]

The serum potassium concentration should always be determined in patients intoxicated with digitalis; if it is less than 4.0 mEq/L, potassium supplements should be administered, preferably in IV fluids. Potassium competes with digitalis for binding sites on the Na^+-K^+-ATPase pump and provides a more suitable environment for the antiarrhythmic agents to work.

Other agents may be beneficial in certain situations. Propranolol may be useful for digitalis-induced ventricular tachyarrhythmia, but not when conduction block is present. Quinidine increases the serum concentration of digoxin and should not be used. Procainamide is less effective than other drugs in treating digitalis-induced arrhythmia. Cholestyramine, a steroid-binding resin, may be useful in cases of digitoxin and early digoxin intoxication.[114] Cholestyramine binds digitalis in the intestinal tract. Digitoxin undergoes enterohepatic circulation and so can be bound by this resin. In contrast, digoxin undergoes minimal enterohepatic circulation, and treatment with cholestyramine is only useful soon after overdose. Cardiac glycoside-specific antibodies have been used to bind digitalis glycosides in the blood stream and thus remove them from myocardial binding sites.[115]

SYMPATHOMIMETIC AMINES

PHARMACODYNAMICS. Sympathomimetic amines increase myocardial contractility by binding to cardiac β-adrenergic receptors.[116] An occupied β-receptor is coupled with stimulatory G protein, G_s, to activate adenyl cyclase within the cell. Adenyl cyclase cleaves adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), which acts as a second messenger by stimulating a cellular protein kinase system. Protein kinases phosphorylate intracellular proteins, such as the sarcoplasmic reticulum, allowing them to bind more calcium during diastole and to release more calcium during systole.[116]

Most sympathomimetic drugs increase contractility about 100 percent above baseline, but many are unsuitable for treating heart failure because of other properties. Sympathomimetic agents stimulate both β- and α-adrenergic receptors. The degree to which each type of receptor is stimulated depends on the specific drug.[117] Isoproterenol is a pure β-adrenergic stimulating agent that increases contractility and heart rate, is arrhythmogenic, and tends to decrease blood pressure. Norepinephrine increases contractility but also stimulates peripheral α-adrenergic receptors. The latter constrict systemic arterioles, which increases blood pressure. Epinephrine increases contractility but causes tachycardia and is arrhythmogenic. None of these drugs are suitable for treating heart failure. Dopamine and dobutamine are more suitable because they are less arrhythmogenic, and they produce smaller increases in heart rate than do other sympathomimetic drugs.[118]

PHARMACOKINETICS. Sympathomimetic drugs have very short half-lives (several minutes) and must be administered IV as a constant-rate infusion. They cannot be given orally because they are metabolized extensively by the liver (first-pass effect).[119] An infusion pump is generally required to deliver these drugs at an appropriate dosage because of the low flow rates needed to avoid excessive plasma volume expansion in patients with heart failure.

Dopamine

Dopamine is the precursor of norepinephrine. It stimulates cardiac β_1-adrenergic receptors as well as peripherally located dopaminergic receptors.[120] The latter appear to be located most prevalently in the renal and mesenteric vascular beds, where they produce vasodilation. Dopamine improves contractility and increases cardiac output in patients with heart failure. At low doses, it causes selective dilatation of arterioles in the renal, mesenteric, coronary, and cerebral vascular beds, increasing blood flow to these areas. At high doses, it causes generalized systemic arteriolar vasoconstriction. In patients with heart failure, the resulting increase in afterload can substantially diminish cardiac output. In some human patients with chronic heart failure, dopamine causes increased ventricular filling pressures and edema formation.[121]

The dosage is 1 to 8 μg/kg/min (5-ml vials containing 40, 80, or 160 mg/ml), diluted in 5 percent dextrose. Doses greater than 8 μg/kg/min result in norepinephrine release and increased peripheral vascular resistance.[122] Higher infusion rates are also more likely to cause tachycardia and cardiac arrhythmia. An initial dose of 2 μg/kg/min may be titrated upward to effect. Dopamine infusions sometimes cause nausea and anorexia. Phlebitis and ischemic tissue necrosis can occur when dopamine is delivered outside the vein.

Dobutamine

Dobutamine is a synthetic catecholamine that stimulates β_1-adrenergic receptors, increasing myocardial

contractility, and weakly stimulates peripheral β_2- and α_1-adrenergic receptors. Since the vascular response to such stimulation is balanced, systemic arterial blood pressure is usually unchanged during dobutamine infusion.[123] Dobutamine is less arrhythmogenic than most other sympathomimetic drugs, and it produces little increase in heart rate. When administered to a patient with acute or chronic myocardial failure, dobutamine increases cardiac output and decreases ventricular diastolic pressure, thereby decreasing edema formation. Dobutamine is used to treat acute, severe heart failure, often in combination with nitroprusside, until inotropic support is no longer needed or until other longer-acting positive inotropic agents, such as digoxin, have taken effect. Dobutamine can also be used to treat acute exacerbations of chronic heart failure requiring acute inotropic support. There is some evidence that intermittent administration of dobutamine to humans with chronic myocardial failure can result in sustained improvement in cardiac function.[121, 125]

Dobutamine is supplied in 20-ml vials containing 250 mg of drug. Following dilution in 5 percent dextrose, it is administered IV by constant-rate infusion, 5 to 20 μg/kg/min. The positive inotropic effect of dobutamine is dosage dependent. Doses of 5 to 15 μg/kg/min are generally adequate. Infusion rates greater than 20 μg/kg/min often produce tachycardia or arrhythmia in dogs. Infusion rates of 5 to 10 μg/kg/min are recommended in cats.

BIPYRIDINE COMPOUNDS

Amrinone and milrinone are bipyridine compounds available only for IV administration. Bipyridine compounds primarily act as inhibitors of phosphodiesterase III,[44, 126] an intracellular enzyme that specifically breaks down cAMP in cardiac myocytes. When phosphodiesterase III is inhibited, intracellular cAMP concentration increases, resulting in greater calcium availability to the contractile proteins. At high doses, amrinone and milrinone may increase contractility by directly altering calcium ion transport.[44, 126] Milrinone is about 30 to 40 times more potent than amrinone. Bipyridine compounds also produce arteriolar dilation, an effect that is probably also mediated by phosphodiesterase inhibition in smooth muscle.[127]

Amrinone

In normal anesthetized dogs, an IV bolus of amrinone (1.0 to 3.0 mg/kg) increases contractility 60 to 100 percent, decreases systemic arterial blood pressure 10 to 30 percent, and increases heart rate 5 to 10 percent. The maximal increase in contractility occurs 5 minutes after injection. The positive inotropic effect decreases by 50 percent within 10 minutes and is dissipated within 20 to 30 minutes, indicating the necessity for constant infusion. Infusion rates of 10 to 100 μg/kg/min increase contractility 30 to 90 percent in anesthetized dogs and 10 to 80 percent in unanesthetized dogs. In the anesthetized dog, infusion of 10 μg/kg/min does not decrease blood pressure, whereas 30 μg/kg/min decreases it 10 percent and 100 μg/kg/min decreases it 30 percent. Heart rate does not increase at 10 μg/kg/min, elevates by 15 percent at 30 μg/kg/min, and increases by 20 percent at 100 μg/kg/min. In anesthetized dogs with drug-induced myocardial failure, amrinone infusions increase contractility 40 to 200 percent above baseline and increase cardiac output by 80 percent. Constant-rate infusions in dogs take about 45 minutes to reach peak effect. In normal cats, amrinone infused at 30 μg/kg/min increases contractility 40 percent above baseline; the peak effect occurs 90 minutes after starting an infusion.[128]

The hemodynamic effects of amrinone have not been studied in dogs or cats with naturally occurring heart failure. Treatment recommendations are based on information obtained from normal dogs. Amrinone (Inocor), 5 mg/ml, 20-ml ampules, is advocated only for short-term administration to animals with severe, decompensated systolic pump failure. The initial dose is 1 to 3 mg/kg as a slow IV bolus followed by constant-rate infusion of 10 to 100 μg/kg/min. One half the initial bolus may be administered 20 to 30 minutes after the first bolus. The same regimen may be effective in the cat.

Amrinone has a wide margin of safety. Exacerbation of ventricular arrhythmia occurs in about 5 percent of dogs treated with milrinone for heart failure, and amrinone is presumed to exert similar effects. Amrinone causes thrombocytopenia and flulike symptoms in a small percentage of humans,[129] but these have not been noted in studies of normal dogs.

Milrinone

Milrinone (Primacor) is currently marketed only for IV administration to human patients and has not been studied in dogs with acute myocardial failure. Clinical evaluation of chronic oral administration has been performed in dogs, but this formulation has not been approved for use in humans or animals. In normal anesthetized dogs, IV milrinone dosed at 30 to 300 μg/kg increases contractility 40 to 120 percent while decreasing diastolic blood pressure 10 to 30 percent.[130] Peak effect occurs within 1 to 2 minutes. Milrinone's effect on contractility is reduced by 50 percent in 10 minutes, and the inotropic effect is essentially gone in 30 minutes. Constant rate IV infusions (1 to 10 μg/kg/min) increase contractility 50 to 140 percent, with peak effect in 10 to 30 minutes. Humans with CHF are treated with a loading dose (50 μg/kg) administered

slowly IV over 10 minutes, followed by maintenance infusion (0.375 to 0.75 μg/kg/min). Guidelines for dogs with CHF have not been published. Dogs generally have a greater hemodynamic response to amrinone and milrinone than do humans.

In normal conscious dogs, milrinone administered orally at 0.10 mg/kg increases contractility 30 percent above baseline; a dose of 0.30 mg/kg increases contractility 50 percent above baseline; and a 1.0 mg/kg dose increases contractility more than 80 percent above baseline. Systemic arterial blood pressure is essentially unchanged at these doses, while heart rate increases up to 30 percent at the 1.0 mg/kg dose. In the normal anesthetized cat, a constant-rate infusion of 1.0 μg/kg/min increases contractility about 40 percent, with peak effect occurring within 30 minutes.

Echocardiographic parameters of dogs with myocardial failure (predominantly DCM) improved during a 4-week treatment regimen with milrinone (0.5 to 1.0 mg/kg q 12 hr PO). Ventricular arrhythmia worsened in a small percentage of dogs.[131] In another study of canine dilated cardiomyopathy, cardiac index increased 54 percent, stroke volume index increased 40 percent, and pulmonary capillary pressure decreased 50 percent. Heart rate increased 11 percent, and left ventricular end-systolic diameter, measured from the M-mode echocardiogram, decreased 9 percent, while blood pressure remained constant, indicating increased contractility.[132]

DIURETICS

These drugs are among the most commonly prescribed cardiac medications, both for acute treatment of pulmonary edema and for chronic maintenance therapy. When used appropriately, diuretics have high efficacy and relatively low and predictable toxicity.

CLASSIFICATION. Diuretics are classified according to their site of action within the nephron (Table 12–3). In general, agents that act on the loop of Henle are the most potent. Three classes of diuretics are used clinically in dogs to treat heart failure: thiazide diuretics, loop diuretics, and potassium-sparing diuretics. They differ in their ability to promote salt and water excretion and in their mechanism of action. The loop diuretics are the most potent and may be used in small doses in functional class II patients and in higher doses in patients in functional classes III and IV heart failure. They are administered orally for chronic therapy or parenterally for acute, severe heart failure. Thiazide diuretics are mildly to moderately potent agents. They are most commonly used in conjunction with a loop diuretic in patients with severe, refractory CHF. Potassium-sparing diuretics are generally reserved for those patients that become hypokalemic with other diuretics, or that are refractory because of an elevated plasma aldosterone concentration. In the latter situation, a potassium-sparing diuretic is usually administered in conjunction with another drug, usually a loop diuretic.

MECHANISMS. Diuretics promote urine flow by increasing renal plasma flow or by altering nephron function. Diuretics that increase renal plasma flow by expanding plasma volume (e.g., mannitol, glucose) are contraindicated in heart failure because they increase venous pressures and edema formation. Agents altering nephron function increase urine production either by interfering with ion transport in the renal tubules or by opposing the action of aldosterone or antidiuretic hormone (ADH) in the kidney. Since the goal of diuretic therapy in heart failure is promotion of salt and water loss, agents that cause only water loss by interfering with ADH are not routinely used. Diuretics interfere with ion transport by altering (1) intracellular ionic entry, (2) energy generation and utilization for ion transport, or (3) ion transfer from the cell

TABLE 12–3
Commonly Used Diuretics

Diuretic Class	*Generic Name*	*Brand Name*	*Mechanism of Action*	*Electrolyte and Acid-Base Effects*	*Adverse Effects, Drug Interactions*	*Dosage Range*
Loop Diuretics	Furosemide	Lasix	Ascending loop of Henle: inhibits Na/K/Cl symport	↑ HCO_3^- ↓ Na^+, Cl^-, K^+, Mg^{++} Metabolic alkalosis	Hypovolemia Ototoxicity NSAIDs (efficacy) Aminoglycosides	1.1–4.4 mg/kg q8–24h (dogs) 0.5–2.2 mg/kg q12h (cats)
Thiazide Diuretics	Chlorothiazide Hydrochlorothiazide	Diuril HydroDIURIL	Distal tubule: Inhibits NaCL symport	↑ HCO_3^-, Ca^{++} ↓ Na^+, Cl^-, K^+, Mg^{++} Metabolic alkalosis	Hyperglycemia Uric acidemia NSAIDs (efficacy)	Diuril: 20–40 mg/kg q12h (dogs) HydroDIURIL: 2.0–4.0 mg/kg q12h (dogs) (given every 3rd day when used with loop diuretics)
Potassium-Sparing Diuretics	Spironolactone	Aldactone	Collecting duct: Aldosterone antagonist	↑ K^+	Gynecomastia ACE inhibitors (hyperkalemia)	1.0–2.0 mg/kg q12h (dogs)
	Triamterene	Dyrenium	Collecting duct: Inhibits Na conductance	↑ K^+, Mg^{++} Metabolic acidosis	ACE inhibitors (hyperkalemia)	1.0–2.0 mg/kg q12h (dogs)

NSAIDs, nonsteroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme.

to the peritubular capillaries through the antiluminal membrane.[133]

Loop Diuretics

These include furosemide, ethacrynic acid, and bumetanide. Furosemide is the most commonly used agent; ethacrynic acid is rarely given. Bumetanide is 40 to 50 times as potent as furosemide and may offer some clinical advantages, most notably more complete absorption with oral dosing.[134] However, its use has not been popularized in dogs and cats. All loop diuretics inhibit active sodium, potassium, and chloride reabsorption in the thick portion of the ascending loop of Henle.[135] In so doing, they inhibit sodium and obligatory water reabsorption in the nephron. The loop diuretics are capable of increasing the maximal fractional excretion of sodium to 23 percent of the filtered load, making them the most powerful natriuretic agents available. In addition to their diuretic effects, they may act as venodilators, decreasing venous pressures shortly after IV administration and before diuresis takes place.[136]

FUROSEMIDE. Furosemide (Lasix, Disal) is supplied as a 10-mg/ml elixir, as 12.5-, 20-, 40-, and 50-mg tablets for oral use,[41] and as a 50-mg/mL solution for IV, subcutaneous, or intramuscular injection. Furosemide is highly protein bound and is not extensively metabolized in the dog and cat. Most is secreted into the proximal tubule, where it acts as a mild carbonic anhydrase inhibitor. Furosemide decreases renal vascular resistance, thereby increasing renal blood flow. When administered IV, its onset of action is 5 minutes, and its peak effect occurs within 30 minutes. Its half-life is 15 minutes, and duration of effect is 2 hours. After oral administration, the onset of action occurs within 60 minutes, its peak effect occurs within 1 to 2 hours, and its effect lasts 6 hours. The oral canine dose ranges from 1 mg/kg every other day to 4 mg/kg q 8 hr, depending on the severity of the clinical signs associated with congestive heart failure and the concurrent use of other drugs. Lower doses (e.g., 1 to 2 mg/kg q 12 hr) should be used in dogs receiving an ACE inhibitor. The dose is always adjusted as low as possible while still controlling congestive signs. Oral furosemide doses in cats range from 1 mg/kg every 2 to 3 days, to 2 mg/kg q 12 hr. We have occasionally used higher doses (4 mg/kg q 12 hr) in refractory CHF.

Severe pulmonary edema requires immediate IV furosemide administration (dogs, 2 to 8 mg/kg q 1 to 2 hr; cats, 2 to 4 mg/kg q 1 to 2 hr). Such intensive dosing may result in hyponatremia, hypokalemia, and dehydration, which must be addressed after the life-threatening pulmonary edema has been controlled. These conditions usually self-correct when the patient eats and drinks. Electrolyte disturbances may result in exacerbation of ventricular arrhythmias, and hypokalemia may induce or potentiate digitalis intoxication. Serious electrolyte disturbances and dehydration are rare in dogs treated with furosemide, but cats are more sensitive. Cats rarely require more than 2 to 4 mg/kg q 2 to 4 hr IV for treatment of severe pulmonary edema.[94]

A number of factors can limit the natriuretic effect of furosemide in patients with heart failure.[137] As a result of progressive reductions in cardiac output, renal blood flow and glomerular filtration decline, decreasing the delivery of furosemide to its site of action. With chronic use of furosemide, the distal tubule hypertrophies, and the rate of sodium reabsorption increases. Nonsteroidal anti-inflammatory drugs (NSAIDs) also reduce the efficacy of furosemide. Several strategies can be used to overcome these limitations. The dose or frequency of administration can be increased, or furosemide can be administered parenterally.[137] Bumetanide is better absorbed orally and can be substituted for furosemide. Alternatively, different classes of diuretics can be combined to block the adaptive responses that limit single-agent therapy.[137, 138]

Thiazide Diuretics

These agents inhibit the Na^+/Cl^- cotransporter in the distal convoluted tubule.[139] The subsequent increase in delivery of Na^+, Cl^-, and water into the collecting duct directly enhances K^+ and H^+ secretion in this location. Thus, thiazide diuretics can induce hypokalemia and metabolic alkalosis. They also act to waste magnesium and increase calcium reabsorption. Only mild-to-moderate renal sodium loss is promoted by thiazide diuretics, about one third to one half that achieved with the loop diuretics. Thiazide diuretics increase renal sodium excretion from a normal value of about 1 percent to 5 to 8 percent of the filtered load. Thiazide diuretics are much less effective when renal blood flow is low, which may explain their lack of efficacy in patients with severe heart failure. Thiazide diuretics are not as effective in patients with renal failure, and they tend to decrease renal blood flow and further compromise renal function.

A synergistic effect results when thiazide diuretics are administered together with loop diuretics.[137, 138] Addition of a thiazide diuretic every 2 or 3 days often resolves refractory pulmonary congestion without causing excessive volume depletion. Hypokalemia is more common in animals treated with furosemide and a thiazide diuretic. This can sometimes be prevented by oral potassium supplementation and/or by adding spironolactone to the therapeutic regimen.

Chlorothiazide and hydrochlorothiazide are the most commonly used thiazide diuretics in dogs and cats. Both are well absorbed after oral administration. The action of chlorothiazide begins within 1 hour,

peaks at 4 hours, and lasts 6 to 12 hours. In dogs, the dosage of chlorothiazide (Diuril), supplied in 250- and 500-mg tablets, is 20 to 40 mg/kg q 12 hr PO. Hydrochlorothiazide has an onset of action within 2 hours, peaks at 4 hours, and lasts 12 hours. The dose of hydrochlorothiazide (HydroDIURIL), supplied in 25- and 50-mg tablets, is 2 to 4 mg/kg q 12 hr PO in dogs, and 1 to 2 mg/kg q 12 hr PO in cats. The newer, more lipid-soluble thiazides, trichloromethiazide and cyclothiazide, have not been studied in the dog or cat.

Potassium-Sparing Diuretics

This class of diuretics includes spironolactone and triamterene. They act by inhibiting the action of aldosterone on distal tubular cells. Their diuretic effect is mild in normal animals because the plasma aldosterone concentration is relatively low. In normal dogs, these drugs increase the maximal fractional excretion of sodium only to 2 percent of the filtered load.[140] These agents are probably more effective in dogs with heart failure and increased plasma aldosterone concentrations. When potassium-sparing diuretics are administered with other diuretics, potassium loss is decreased. They are often administered to patients that become hypokalemic because of another diuretic agent.

Spironolactone is well absorbed from the gastrointestinal tract (62 percent), and it is extensively and rapidly metabolized to the active product, canrenone.[141] Canrenone is structurally similar to aldosterone, and its effects result from competitive binding to aldosterone's binding sites in the distal tubule. Spironolactone has a slow onset of action, and its peak effect does not occur until 2 to 3 days after administration. The use of spironolactone for CHF has been advocated for several other reasons. It is theorized that spironolactone can reduce myocardial fibrosis in patients with heart disease, and it may help restore normal baroreceptor function in heart failure.[142] The clinical importance of these effects is not known. The dose of spironolactone (Aldactone), supplied in 25-mg tablets, is 2 to 4 mg/kg/day PO in dogs.

Triamterene competitively displaces aldosterone from its binding sites and directly inhibits the distal tubular transport of potassium.[143] Its action begins within 2 hours, peaks at 6 to 8 hours, and lasts 12 to 16 hours. In dogs, the dose is 2 to 4 mg/kg/day PO. It is used only rarely in dogs or cats with heart failure.

LOW-SODIUM DIETS

A diet low in sodium is one means of reducing circulating blood volume. Sodium is retained in heart failure patients by a variety of mechanisms, including activation of the renin-angiotensin-aldosterone system. Diuretic therapy as a modality for reducing total body sodium and blood volume has been discussed previously. Patients with severe heart failure that are refractory to diuretic administration have the greatest need for a low-sodium diet. Patients with early and mild heart failure generally do not need marked salt restriction. Chapter 32 details the dietary and sodium requirements in heart failure.

VASODILATORS AND ACE INHIBITORS

A number of different drugs relax arteriolar or venous smooth muscle to cause vasodilation (Table 12–4). Vasodilators are generally classified as arteriolar

TABLE 12–4
Commonly Used Vasodilators

Group	*Generic Name*	*Brand Name*	*Mechanism of Action*	*Venous Dilation*	*Arteriolar Dilation*	*Dosage Range**
Direct Acting	Hydralazine	Apresoline	Uncertain	+	+ + +	0.5–3.0 mg/kg q12h (dogs)
Nitrates	Nitroprusside	Nipride	Nitric oxide donors	+ + +	+ + +	2.0–5.0 µg/kg/min (dogs)
	Nitroglycerin (2%)	Nitro-Bid, Nitrol		+ + +	+	1/2″/5.0 kg q8h (cats, dogs)
	Nitroglycerin patch	Nitro-Dur		+ + +	+	0.1–0.2 mg/hr (cats, dogs)
	Isosorbide dinitrate	Isordil		+ + +	+	0.2–2.0 mg/kg q12h (dogs)
	Isosorbide mononitrate	Monoket, Imdur		+ + +	+	0.2–2.0 mg/kg q12h (dogs)
Calcium Channel Blocking Drugs	Amlodipine	Norvasc	Inhibit L-type, voltage-sensitive, calcium channels	+	+ + +	0.05–0.20 mg/kg q24h (dogs) 0.625 mg q24h (cats < 5 kg) 1.25 mg q24h (cats > 5 kg)
Adrenergic Receptor Blocking Drugs	Prazosin	Minipress	Alpha₁-adrenergic receptor antagonists	+ + +	+	1.0 mg q8h (dogs < 15 kg) 2.0 mg q8h (dogs > 15 kg)
ACE Inhibitors	Benazepril	Lotensin	Inhibit generation of angiotensin II	+ +	+ +	0.25 mg/kg q24h (cats, dogs)
	Enalapril	Enacard, Vasotec	Decrease bradykinin metabolism	+ +	+ +	0.5 mg/kg q12–24h (dogs)
	Lisinopril	Prinivil, Zestril		+ +	+ +	0.5 mg/kg q12–24h (dogs)

*See text for discussion.
ACE, angiotensin-converting enzyme.

dilators, venodilators, or combination (balanced) arteriolar and venodilators. The effect of a particular agent depends on (1) the vascular bed(s) it influences (systemic, pulmonary, or both), and (2) its relative potency in these locations. With a few exceptions, the effect of these drugs on the pulmonary vasculature is erratic or insignificant relative to their action on the systemic vascular bed.

Arteriolar vasodilators relax the smooth muscle of systemic arterioles, decreasing peripheral vascular resistance or impedance. This decreases systemic arterial blood pressure, systolic intraventricular pressure, and systolic myocardial wall stress (afterload). When the force that opposes myocardial fiber shortening is reduced, myocardial cells can shorten further, and stroke volume increases. This is the desired and primary effect when these drugs are administered to patients with dilated cardiomyopathy. In animals with mitral regurgitation or intracardiac or vascular shunts beyond the atrial level, arteriolar vasodilators also reduce regurgitant and shunt blood flow. In animals with severe mitral regurgitation, regurgitant flow is reduced because of diminution in the size of the regurgitant orifice and reduction of the LV-LA pressure gradient. Decreased regurgitant flow results in reduced left atrial pressure, pulmonary capillary pressure, and pulmonary edema formation.

Venodilators relax systemic venous smooth muscle, decreasing systemic venous pressure and increasing the capacitance of the systemic venous reservoir. The resulting redistribution of blood from the heart and pulmonary veins reduces ventricular diastolic and pulmonary venous pressures, causing diminished edema formation. Venodilators are used in the same situations as diuretics and low-sodium diets.

AMLODIPINE

Amlodipine (Norvasc) acts predominantly as an arteriolar vasodilator.[111] It is a member of the 1,4-dihydropyridine family of calcium channel blocking drugs. In humans, amlodipine reduces the symptoms of heart failure, substantially improving exercise tolerance in most patients.[145] In contrast to many other calcium channel blocking drugs, amlodipine does not increase cardiovascular morbidity or mortality. In a recent study, amlodipine prolonged survival in humans with dilated cardiomyopathy.[115] The safety and efficacy of this compound in dogs with dilated cardiomyopathy or degenerative valve disease have not yet been determined. Preliminary observations suggest that amlodipine may be efficacious in dogs with either of these conditions. Amlodipine is also efficacious for the treatment of systemic hypertension in cats (chapter 35).

With oral administration, amlodipine's peak effect is observed in 4 to 7 days, reflecting its 30-hour half-life in dogs.[144, 146] In experimental studies, once-daily treatment of renal hypertensive dogs using oral amlodipine at 0.05 mg/kg caused a substantial reduction (20 mmHg) in mean arterial blood pressure.[144] Chronic, once-daily administration of amlodipine (0.2 mg/kg PO) lowered blood pressure without causing tachycardia. Administration of a single 1.0 mg/kg oral dose to hypertensive dogs reduced blood pressure (a 30-mmHg decline) with a peak effect 8 hours postadministration. This dosage caused reflex tachycardia that could be abolished by simultaneous administration of a β-receptor blocking drug. In another experiment involving dogs with experimental renal hypertension, systolic and diastolic blood pressure declined by 30 mmHg following a single oral dose of 0.3 to 0.4 mg/kg.[146]

A safe and effective dose of amlodipine for treating dogs or cats with heart failure has not been established. Based on our own preliminary results, it is reasonable to attempt to palliate chronic, refractory heart failure in dogs using amlodipine at an initial dose of 0.05 mg/kg PO bid, and titrating upward to 0.20 mg/kg, depending on the response. Arterial blood pressure should be monitored 6 to 8 hours after the initial dose and at intervals until the peak effect is observed 5 to 7 days later. Amlodipine is supplied as 2.5-mg tablets.

HYDRALAZINE

Hydralazine (Apresoline) is a pure arteriolar vasodilator that probably acts by increasing the prostacyclin concentration in systemic arterioles.[147] Hydralazine decreases resistance in renal, coronary, cerebral, and mesenteric vascular beds more than in skeletal muscle beds.[148] Increased renal blood flow can improve renal function (if initially depressed) and thereby enhance digoxin excretion and improve furosemide delivery to the nephron.[149] The effects of orally administered hydralazine have been studied in dogs.[150, 151] Hydralazine is well absorbed from the gastrointestinal tract but undergoes first-pass hepatic metabolism by acetylation.[152] Although hydralazine is not excreted by the kidney, its biotransformation is affected by renal failure, which may increase serum concentration.

The vasodilating effect occurs within 1 hour after oral administration and peaks within 3 hours. The effect is then stable for the next 8 to 10 hours, after which it rapidly dissipates. The net duration of effect is about 12 hours.[151] Hydralazine decreases regurgitant flow, increases forward aortic flow and venous oxygen tension, and decreases radiographic evidence of pulmonary edema in dogs with mitral regurgitation.[150, 153] Therapeutic dosage decreases mean arterial blood pressure from 100 to 110 mmHg to 60 to 80 mmHg. These effects improve the quality of life and may prolong survival time. In dogs with dilated cardiomyopathy, hydralazine improves cardiac output but usually does not decrease pulmonary edema. In humans, com-

bined use of hydralazine and isosorbide dinitrate improves survival and the quality of life.[24]

Clinical use of hydralazine is generally limited to dogs that do not tolerate ACE inhibitors or that become refractory to conventional heart failure therapy (i.e., digoxin, furosemide, an ACE inhibitor, and low salt diet). Hydralazine can also be used to treat dogs with acute, fulminating congestive left-sided heart failure secondary to severe mitral regurgitation when nitroprusside infusion is not possible. Its rapid onset of action and short half-life make hydralazine a better choice than amlodipine for this purpose.

The hemodynamic effects of hydralazine are dose dependent, and overdosing can result in serious hypotension, particularly when administered to a dog already receiving an ACE inhibitor. Consequently, the dose must be titrated carefully, starting low and gradually increasing until clinical or hemodynamic improvement is noted. Systemic arterial blood pressure should be measured either by invasive or noninvasive methods in this circumstance. Hydralazine is supplied in 10- and 25-mg tablets. A dose of 0.5 mg/kg PO should be administered initially to dogs in heart failure due to severe mitral regurgitation. An effective dose is confirmed by a decrease in systolic or mean systemic arterial blood pressure of 15 to 30 mmHg. Clinically, reduced capillary refill time, pinker mucous membranes, and regression of pulmonary edema suggest efficacy. If the initial dose is not effective, it is titrated gradually upward (increments of 0.5 mg/kg) until a beneficial effect is documented or a total dose of 3.0 mg/kg q 12 hr is achieved.

In dogs with acute, fulminating heart failure due to severe mitral regurgitation that are not already receiving an ACE inhibitor, hydralazine titration can be more aggressive. An initial dose of 2.0 mg/kg may be administered initially along with IV furosemide. Blood pressure monitoring is strongly encouraged, because this dose may produce hypotension. The risks of treatment are well warranted in patients with life-threatening pulmonary edema.

Hydralazine can cause reflex tachycardia, particularly when blood pressure declines in patients with low plasma catecholamine concentrations. Hydralazine-mediated histamine release contributes to the tachycardia by stimulating norepinephrine release. Patients with elevated plasma catecholamine concentrations may not experience tachycardia when hydralazine is administered. When dogs with congestive heart failure are treated with hydralazine, about one third of the dogs experience tachycardia, one third have no change in heart rate, and one third experience a decrease in heart rate. Digoxin can be administered to help control hydralazine's tendency to increase heart rate.

Hydralazine causes vomiting in some dogs. Reducing the dose to 0.25 to 0.5 mg/kg q 12 hr for 1 or 2 weeks and then increasing the dose to its therapeutic range may be effective in resolving this complication. In other cases, persistent vomiting necessitates the use of a different vasodilator. Hydralazine's most serious adverse effect is hypotension. Mild hypotension, indicated clinically by signs of weakness and depression, does not require treatment. Such signs will abate within 10 to 12 hours after the last dose of hydralazine. The dose should then be reduced.

Other direct-acting vasodilators that act independently of the calcium channel include endralazine, cadralazine, minoxidil, dipyridamole, and pinacidil. None have been evaluated in dogs or cats with heart failure.

ALPHA-ADRENERGIC BLOCKING AGENTS

Prazosin

Prazosin (Minipress) is an arteriolar and venodilating agent. It acts primarily by blocking α_1-adrenergic receptors and also peripherally inhibits phosphodiesterase.[154] Since prazosin does not block α_2-adrenergic receptors, norepinephrine release is still controlled via negative feedback. Reflex tachycardia is generally not seen. The vasodilating effects of prazosin become attenuated after the first dose in humans[155] and in rats.[156] In rats, it is thought that this effect is brought about by stimulation of the renin-angiotensin-aldosterone system. Thus, concurrent use of an ACE inhibitor may blunt the development of resistance.

The hemodynamic effects of prazosin have not been documented in the dog or cat. In humans, its administration decreases right and left ventricular filling pressures, edema, and congestion and increases stroke volume and cardiac output.[157] Prazosin is supplied in capsules containing 1, 2, and 5 mg of drug. The starting dose in dogs is 1 mg q 8 hr for dogs weighing less than 15 kg, and 2 mg q 8 hr for dogs weighing more than 15 kg. This is then titrated upward if the initial dose is ineffective, or reduced if hypotension occurs. Prazosin has not been used in cats. Other α-adrenergic receptor blocking drugs used in humans (bunazosin, doxazosin, indoramin, terazosin, trimazosin, and urapidil) have not been evaluated in cats or dogs.

NITRATES

Nitroglycerin

Nitroglycerin and the organic nitrates act primarily as venous and coronary artery vasodilators, with a less pronounced effect on the systemic arterioles.[158] Nitroglycerin ointment (Nitrol or Nitro-Bid) is available in a 2 percent formulation to be spread on the skin for absorption into the systemic circulation. It is also supplied in a transdermal patch preparation. In dogs and cats, a 2 percent nitroglycerin cream is often used (1/2 to 2 inches every 4 to 6 hours for dogs, 1/8 to

1/4 inch every 4 to 6 hours for cats), but the efficacy of this treatment has not been documented.[159] In human patients, the absorption of cutaneously applied nitroglycerin varies with the site and area of application, as well as the amount of ointment used. These variables have not been studied in dogs or cats. Humans can adjust the dose and method of application to obtain the desired effect, but such adjustments are not possible in dogs and cats. If transdermal nitroglycerin cream is used, it should be applied on a hairless or shaved area, using gloves to avoid human transdermal absorption. To ensure more uniform dosing, self-adhesive transdermal nitroglycerin patches have also been used in dogs and cats with CHF. Patches delivering 0.1 mg/hr have been recommended for treating cats and small dogs, and patches delivering 0.2 mg/hr were recommended for larger dogs.[41]

Isosorbide Dinitrate

Orally administered organic nitrates may be preferred for the foregoing reasons. Unfortunately, appropriate doses of these compounds are not well established. Isosorbide dinitrate is available in a sublingual formulation, in a standard oral formulation, and as a controlled-release capsule and tablet. An empiric dose of the standard oral formulation (Isordil) that has been used for dogs is 0.22 to 0.44 mg/kg given every 8 hours.[160] In dogs with experimentally created myocardial infarcts, isosorbide dinitrate has been dosed as high as 2.0 mg/kg bid.[161] Isosorbide mononitrate, the primary metabolite of isosorbide dinitrate, can also be used in dogs with heart failure.[162, 163] From these studies, the estimated oral dose of isosorbide mononitrate in dogs is 0.25 to 2.0 mg/kg, with a dosing interval of 6 to 12 hours. In humans, a dosage-free interval, typically 10 to 12 hours long, is advised to avoid the phenomenon of tolerance. The utility of this maneuver in dogs or cats with CHF is unknown.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The efficacy of ACE inhibiting drugs has been convincingly demonstrated in human patients with CHF. These drugs have been shown to improve hemodynamic function and to improve clinical symptoms in patients with mild, moderate, and severe heart failure.[21–24, 49, 164] The hemodynamic effects of ACE inhibitors are modest in relation to the potent effects of some direct-acting vasodilators, such as hydralazine and nitroprusside. Similarly, the diuretic effect of ACE inhibiting drugs is modest in relation to the potent effect of furosemide. For these reasons, ACE inhibiting drugs are not indicated for the treatment of acute heart failure. Their intended application is the treatment of chronic heart failure, and for this purpose they are more effective than other vasodilating drugs. ACE inhibiting drugs delay the onset of heart failure in human patients with asymptomatic left ventricular dysfunction, and they reduce overall mortality from cardiovascular disease in those patients in overt heart failure (classes II, III, and IV).[21–24]

Of the many ACE inhibitors available for use, captopril, enalapril, lisinopril, benazepril, quinapril, and ramipril have been studied in dogs with naturally occurring heart failure.[52, 165–169] Enalapril has been studied most thoroughly, and it is the only ACE inhibiting drug that is specifically approved in the United States for treating heart failure in dogs. Enalapril, benazepril, quinapril, and ramipril are prodrugs that are converted to their active form in the liver, whereas captopril and lisinopril are active drugs.[170] This distinction is not particularly important, since the conversion of prodrugs to an active form does not limit drug availability even in patients with severe liver disease. With the exception of ramipril, all the ACE inhibitors listed are eliminated primarily via the kidney.[170, 171] Lisinopril is eliminated entirely via glomerular filtration, whereas the others are eliminated by glomerular filtration and renal tubular secretion. The rate of elimination of these drugs declines with decreased kidney function, indicating the necessity for dosage adjustment when renal function is severely impaired.

It is difficult to determine the optimal dose for any ACE inhibitor or to compare relative efficacy. The degree and duration of inhibition of plasma ACE activity are commonly assayed. However, it is unknown to what degree or how long plasma ACE activity must be inhibited before a beneficial therapeutic effect is observed. Moreover, the degree to which ACE inhibitors inhibit plasma and tissue ACE activity varies both in magnitude and in duration; the significance of these differences relative to clinical efficacy is uncertain.

MECHANISMS. ACE inhibitors reduce the activity of ACE in the body by binding with its zinc ion–containing active site.[165] ACE cleaves two peptides off the decapeptide angiotensin I to create the octapeptide angiotensin. In this fashion, inhibition of ACE decreases circulating concentrations of angiotensin II (Fig. 12–9). Angiotensin II is a very potent vasoconstrictor that helps maintain systemic arterial blood pressure in heart failure patients. A decreased plasma angiotensin II concentration allows the systemic arterioles and veins to relax (dilate). Angiotensin II also stimulates sodium and water retention indirectly via release of aldosterone from the adrenal gland. With ACE inhibition, the elevated plasma concentration of aldosterone declines, promoting renal sodium and water excretion. Accumulation of bradykinin in the tissues may contribute to the observed hemodynamic and cardiovascular effects of ACE inhibiting drugs.

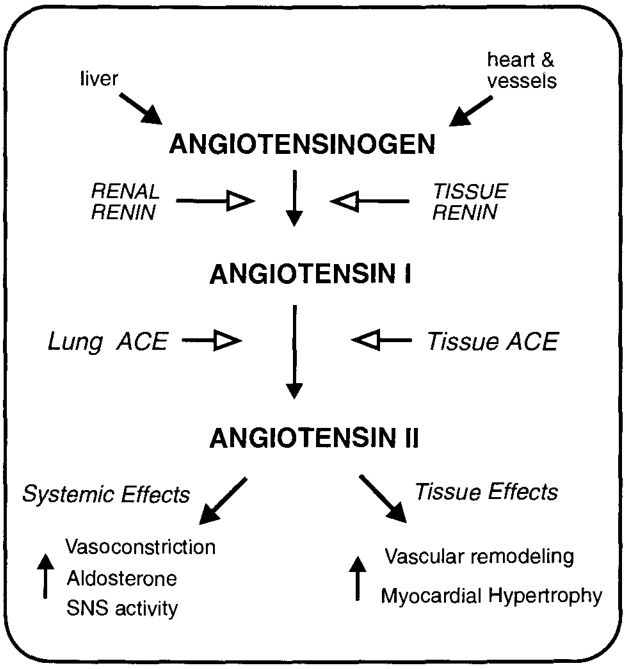


FIGURE 12–9

The *renin-angiotensin system* is composed of circulating (systemic) and tissue components. Changes in blood volume and peripheral vascular resistance are modified primarily by the renin-angiotensin system. Reduced renal perfusion is the primary stimulus for renin release by the kidney and activation of the systemic renin-angiotensin-aldosterone mechanism. The tissue angiotensin system may be activated even earlier than the systemic angiotensin system. Some tissues also contain proteases that can act on angiotensin I to produce angiotensin II (the chymase pathway). Tissue angiotensin II is thought to be a stimulus of myocardial hypertrophy, fibroblast proliferation, and remodeling of the coronary and systemic vasculature. ACE inhibiting drugs can decrease the formation of angiotensin II in all these locations, but they do not block the chymase pathway. ACE, angiotensin-converting enzyme; SNS, sympathetic nervous system.

ACE also inactivates bradykinin, which induces vasodilation directly and indirectly by increasing production of the prostaglandins PGI_2 (prostacyclin) and PGE_2.

Local renin-angiotensin systems have been demonstrated in a number of different organs and tissues, including the kidney, brain, blood vessels, myocardium, and the cardiac valves.[49, 172] These local renin-angiotensin systems are believed to regulate cellular growth, thereby mediating the development of the vascular changes and ventricular remodeling processes observed in patients with heart disease. Inhibition of vascular and ventricular remodeling might protect against the progressive deterioration of ventricular function in patients with heart disease. Some investigators have suggested that the beneficial effects of ACE inhibiting drugs, including increased survival, are due to inhibition of tissue ACE rather than their diuretic or hemodynamic effects.

CAPTOPRIL. This sulfhydryl-containing ACE inhibitor was the first compound in this class used to treat patients with heart failure. The bioavailability of captopril is about 75 percent in fasted dogs, but it is reduced by 30 to 40 percent when there is food in the gastrointestinal tract.[173] Captopril has a rapid onset of action relative to other ACE inhibitors, and it begins to exert hemodynamic effects within an hour after oral administration; its peak effect occurs approximately 1 to 2 hours postadministration.[174] Thereafter, the ACE inhibiting activity of captopril declines rapidly as the compound is rapidly excreted. In one study, a single 2.0 mg/kg oral dose of captopril reduced plasma ACE levels by less than 50 percent (peak effect) in normal dogs, and plasma ACE levels returned to normal 3 hours after administration.[175] Other studies suggest much higher levels of ACE inhibition, with a markedly diminished response after 6 hours.[176] The recommended dose of captopril in dogs with heart failure is 2.0 mg/kg q 8 hr. Captopril is rarely used in dogs because of its short duration of action and reports of persistent anorexia. Carefully controlled clinical trials in dogs or cats with heart failure have not been performed.

ENALAPRIL. This prodrug has very little ACE activity until it is converted (hydrolyzed) in the liver to the active diacid enalaprilat.[170] Enalapril is well absorbed in dogs, and estimates of its bioavailability range from 60 to 70 percent with oral administration.[177] The peak concentration of enalaprilat is attained 2 to 4 hours after the oral administration of enalapril. At recommended dosages of enalapril (0.5 mg/kg), plasma ACE activity is reduced by 75 percent 3 hours after the first oral dose in healthy dogs.[175] Plasma ACE activity is still reduced, albeit to a lesser extent, 12 hours postdosing. Plasma ACE inhibition is minimal 24 hours after a single oral dose. Clinical improvement has been demonstrated in dogs with heart failure when enalapril is administered at 0.5 mg/kg once daily.[52] Hemodynamic studies, studies of plasma ACE inhibiting activity, and clinical trials indicate that enalapril is most effective when it is given twice daily.[52]

The Cooperative Veterinary Enalapril (COVE) study group reported that enalapril, used in combination with digoxin and furosemide, significantly reduces the clinical signs of heart failure and improves exercise tolerance in dogs with congestive heart failure from DCM or mitral regurgitation.[52] The Invasive Multicenter Prospective Veterinary Enalapril (IMPROVE) study group reported that enalapril, dosed at 0.5 mg/kg q 12 hr, produces a significant decline in pulmonary capillary wedge pressure (PCWP) in dogs with heart failure caused by DCM.[166] In this study, the decline in PCWP was less marked in dogs with mitral regurgitation. In both groups, the clinical signs of heart failure and the radiographic severity of pulmonary edema were significantly reduced by treatment with enalapril. Enalapril's effect on survival has not been directly

measured in dogs with naturally occurring heart failure. Controlled studies have shown that enalapril significantly increases the time to development of refractory heart failure or death in dogs with dilated cardiomyopathy.[52, 178] This effect has not been convincingly demonstrated in dogs with mitral regurgitation.[52, 178]

LISINOPRIL. Lisinopril is somewhat more potent than enalapril, and its duration of action is slightly longer than that of enalapril.[179] The bioavailability of lisinopril is somewhere between 25 and 50 percent, and it is not affected by feeding.[170, 180] Following a single oral dose of lisinopril (0.5 mg/kg), plasma ACE activity is reduced by 75 percent 3 hours later, and ACE activity is still reduced 12 hours postdosing.[175] Plasma ACE inhibition is minimal 24 hours after a single 0.5 mg/kg oral dose. The hemodynamic effects have been studied in a small number of dogs with class IV heart failure due to dilated cardiomyopathy (Sisson, unpublished). Lisinopril produced a substantial reduction in pulmonary capillary wedge pressure, mean pulmonary artery pressure, systemic arterial pressure, and systemic vascular resistance. Heart rate decreased while stroke volume and cardiac output increased modestly. Five of the seven dogs improved by one or more classes of heart failure following 3 weeks of treatment with once-daily lisinopril (0.5 mg/kg). Blood urea nitrogen concentration rose transiently 1 week after the initiation of treatment but returned to normal after 3 weeks of treatment. No adverse drug effects were noted during this short-term study. The recommended oral dose for dogs is 0.5 mg/kg q 12 to 24 hr. The relative merits of once- versus twice-daily dosing have not been studied, but they are probably similar to those of enalapril.

BENAZEPRIL. This prodrug is readily absorbed and rapidly converted by the liver to the active diacid benazeprilat.[172] In dogs and cats, the peak benazeprilat concentration is attained within 2 hours of oral administration. In one study, a single oral dose of benazepril (0.5 mg/kg) reduced plasma ACE activity in dogs more than 75 percent by 1.5 hours after administration;[175] the plasma ACE concentration was still inhibited 12 hours after dosing but not at 24 hours posttreatment. In apparent contradiction, another study indicated that profound plasma ACE inhibition is present 24 hours following a single 0.25 mg/kg oral dose of benazepril.[181] At steady state, an oral dose of 0.25 mg/kg produced more than 95 percent inhibition of ACE activity at peak effect (2 hours postdosing), and more than 80 percent inhibition of ACE activity 24 hours after dosing. In cats, once-daily oral dosing at 0.25 mg/kg produced 100 percent inhibition of ACE at peak effect and over 90 percent inhibition after 24 hours.[182] In clinical trials conducted in Europe, benazepril was reported to be effective in dogs when administered orally at 0.25 to 0.50 mg/kg q 24 hr.[169]

Adverse Effects of ACE Inhibitors

Enalapril is the only ACE inhibitor to be evaluated for safety and efficacy in large numbers of dogs with congestive heart failure. The majority of adverse reactions observed in controlled clinical trials of enalapril were mild and similar to those observed in dogs receiving placebo.[52, 165, 166] Reported adverse effects of ACE inhibiting drugs include systemic hypotension, hyperkalemia, and azotemia. Systemic hypotension is infrequently observed and can be easily managed by reducing the ACE inhibitor dose. Serious hypotension is most likely to occur in dogs with severe heart failure when other vasodilating drugs are used in combination with an ACE inhibitor. Hyperkalemia is occasionally detected in dogs receiving ACE inhibiting drugs, but it is rarely severe enough to produce clinical signs. Hyperkalemia is presumed to result from reduced glomerular filtration and diminished plasma aldosterone concentrations. Severe hyperkalemia should prompt discontinuation or reduction in ACE inhibitor dose. It is prudent to monitor serum potassium concentration in dogs treated with ACE inhibitors and spironolactone. Potassium-sparing diuretics should be discontinued in those dogs that develop hyperkalemia. In our experience, spironolactone is well tolerated by most dogs treated with an ACE inhibitor and furosemide.

Treatment with ACE inhibitors may precipitate serious renal dysfunction when used with high doses of diuretics, and this complication can be fatal. Mild azotemia is commonly detected in dogs with CHF, particularly when they are aged. Azotemia is usually interpreted as evidence of decreased renal perfusion (prerenal azotemia), combined with an age-related decline in renal functional capacity. ACE inhibitors are known to decrease glomerular filtration pressure by virtue of their effects on the renal afferent and efferent arterioles. Treatment with an ACE inhibitor can and often does result in mild azotemia and slightly increased serum creatinine concentration.[183] Renal function usually soon normalizes or stabilizes at a new steady state.

A small percentage of dogs treated with ACE inhibitors develop life-threatening renal dysfunction.[165, 184] The occurrence of this complication is unpredictable, but it seems to occur most often in dogs with severe heart failure and that become dehydrated (particularly with overdiuresis) or hypotensive. In our experience, serious renal dysfunction occurs most often within 1 week of initiating treatment, but some dogs do not experience the problem for several months. Several precautions should be observed to avoid this problem. Renal function should be assessed prior to initiating an ACE inhibitor. Alternative therapies should be con-

sidered if the serum creatinine concentration exceeds 2.5 mg/dl or the BUN concentration exceeds 50 mg/dl. High furosemide doses (> 4.4 mg/kg/day) should be avoided when initiating ACE inhibitor therapy. Renal function should always be reassessed 5 to 7 days after initiating an ACE inhibiting drug. If serum creatinine concentrations exceed 2.5 to 3.0 mg/dl and BUN concentrations exceed 60 to 70 mg/dl, the ACE inhibitor should be discontinued for 1 to 2 days. Dehydrated patients should be carefully rehydrated and the diuretic regimen reduced. When renal function improves, the ACE inhibitor can be reintroduced at a lower dose or other drug treatments prescribed, typically hydralazine or amlodipine in combination with a nitrate.

BETA-ADRENERGIC BLOCKING DRUGS

Beta-blocking drugs are used to treat many different cardiovascular conditions.[185] Principal indications include supraventricular tachyarrhythmias (chapters 18, 19) (such as atrial fibrillation, atrial tachycardia, and sinus tachycardia when it causes or contributes to impaired ventricular filling); ventricular tachyarrhythmias, either as monotherapy in cats or in combination with other agents; reduction of dynamic outflow tract obstruction (chapter 28); and treatment of systemic hypertension (usually in combination with other drugs) (chapter 35).

Beta-adrenergic receptors are classified into β_1 and β_2 subtypes.[185–187] Cardiac β_1-receptors mediate increases in heart rate, atrioventricular conduction velocity, and myocardial contractility. Stimulation of cardiac β_2-receptors also increases contractility. Beta$_2$-receptors located in vascular and bronchial smooth muscle mediate vasodilation and bronchodilation. Other β_2-receptors mediate renin and insulin release. The number and activity of myocardial β_1-receptors decline in patients with chronic heart failure, presumably in response to exposure to increased levels of catecholamines. In addition, the contractile response to β_2-agonists is reduced.[185, 186] Of the many available β-receptor blocking drugs, propranolol and atenolol are used most often.

Mounting evidence indicates that β-blockers might play a substantive role in the treatment of patients with systolic heart failure.[186, 187] Long-term therapy with high doses of β-adrenergic blocking drugs improves symptoms, exercise tolerance, hemodynamics, left ventricular function, and perhaps even mortality in *some* humans with heart failure, particularly dilated cardiomyopathy. Graduated-dose protocols using metoprolol or bisoprolol reduced the rate of hospitalization for heart failure and improved left ventricular ejection fraction in some patients.[188, 189] In these studies, bisoprolol, but not metoprolol, both of which are β_1-receptor blocking drugs, reduced mortality in patients with DCM. Although these results are encouraging, many heart failure patients did not tolerate even the small initial drug doses administered at the onset of therapy. This subset of patients experienced rapid cardiac decompensation and worsening congestive signs, and some died. There is no reliable way of identifying which patients will respond favorably.

MECHANISM. The mechanism by which some patients benefit from β-blocker therapy is unknown.[190, 191] Some theorize that β_1-receptors, down regulated due to constant exposure to increased norepinephrine, up regulate following prolonged treatment with high doses of β-blocking drugs. Others theorize that long-term β-blocker treatment suppresses the increase in inhibitory G_i protein activity occurring in patients with DCM. Other possible mechanisms include improved ventricular-arterial coupling, structural ventricular remodeling, reduced heart rate, decreased oxygen consumption, more efficient oxygen utilization, as well as the antiarrhythmic effects of β-blockers.

PROPRANOLOL. This nonselective (first generation) agent blocks both β_1- and β_2-receptors. It has poor oral bioavailability,[187] is primarily eliminated by hepatic metabolism, and has a short plasma half-life (0.5 hour in cats, 0.6 to 1.5 hours in dogs), necessitating frequent (q 8 hr) administration. Propranolol is usually used at a dose of 0.25 to 2.0 mg/kg q 8 hr PO, starting low and titrating upward to effect.[41, 185]

ATENOLOL. This selective β_1-blocking drug (second generation) has good oral bioavailability,[192] is eliminated by renal excretion and hepatic metabolism, and has a much longer plasma half-life (3.6 hours in cats and 3.2 to 4.5 hours in dogs) than propranolol. In cats with hypertrophic cardiomyopathy, atenolol (Tenormin) is given initially at a dose of 6.25 to 12.5 mg/cat q 12 to 24 hr PO. Higher doses may be required to achieve a desired effect. Dogs are treated with doses ranging from 12.5 to 50 mg q 12 to 24 hr PO.

OTHER β-BLOCKERS. Carvedilol, which exhibits both α_1- and β_1-receptor blocking activity, has recently been approved for the treatment of heart failure in human patients. Carvedilol improves symptoms and submaximal exercise capacity and reduces mortality in some patients with heart failure caused by dilated cardiomyopathy and ischemic heart disease.[193] It was hoped that carvedilol would be better tolerated in patients with heart failure by virtue of its vasodilating effect. However, it is not tolerated in up to a third of treated patients. Metoprolol (Lopressor) exhibits moderate bioavailability and lipophilicity, is eliminated by hepatic metabolism, and has an approximate elimination half-life of 1.3 hours in the cat and 1.6 hours in the

dog. In canines, it has been used at a dosage of 5 to 50 mg q 8 hr PO. In an experimental canine model of chronic heart failure, metoprolol (25 mg q 12 hr PO) produced beneficial effects (decreased LV end-diastolic pressure, end-diastolic wall stress and stiffness, and improved left atrial contribution to ventricular filling).[194] Nadolol (Corgard) has low oral bioavailability, is poorly lipid soluble, and is eliminated by renal excretion. In the dog, it is given at a dose of 5 to 40 mg q 8 to 12 hr PO.[185]

Adverse Effects with β-Adrenergic Receptor Blockers

Adverse effects common to all β-blockers include bradycardia, hypotension, depression, and precipitation of congestive heart failure.[185] Hypoglycemia in diabetics and bronchospasm in patients with pre-existing lung disease are less likely to develop when selective β_1-agents are used. When β-blocker treatment is discontinued, drug administration should be gradually reduced over several days to avoid withdrawal reactions, such as persistent tachycardia and precipitation of myocardial ischemia. The beneficial effects of chronic, high-dose β-blocker therapy have not yet been demonstrated in dogs or cats with naturally occurring heart failure. Therefore, in these circumstances, its use should be closely monitored.

CALCIUM CHANNEL BLOCKERS

These drugs are used most commonly in the treatment of supraventricular arrhythmias (chapters 18, 19), hypertension (chapter 35), and feline HCM (chapter 28). The use of some calcium channel blockers such as amlodipine to augment vasodilation induced by ACE inhibitors is being evaluated in human trials.[195] This combination therapy exerts synergistic hemodynamic, antiproliferative, and antithrombotic properties.[196] True benefits await verification in veterinary clinical trials.

DILTIAZEM. Diltiazem belongs to the benzothiazepine class of calcium channel blockers and has been used primarily to treat cats with hypertrophic cardiomyopathy and dogs and cats with certain supraventricular tachyarrhythmias. It is available for IV injection, as a standard oral formulation, and in several different extended-release forms. The bioavailability of the standard formulation is 43 percent in dogs and 71 percent in cats.[197, 198] This difference is due to more rapid hepatic metabolism in dogs (first-pass effect).

The pharmacology of diltiazem is complex. In the dog, it is metabolized by the liver into several different active compounds, and it also undergoes enterohepatic recirculation. In cats, peak concentrations of diltiazem are reached in 45 minutes, and its half-life is slightly less than 2 hours.[197] The oral dose of the standard formulation of diltiazem (Cardizem) is 0.5 to 1.5 mg/kg q 8 hr in dogs and cats.[199] The pharmacokinetics of one extended release form of diltiazem (Cardizem CD) has been studied in cats;[198] peak concentration is realized in 140 minutes after oral administration, and half-life is about 7 hours. The recommended oral dose of Cardizem CD in cats is 10 mg/kg once daily.[198] Dilacor is another long-acting diltiazem preparation that has been used in felines.[200] Dilacor capsules of varying strengths contain two to four tablets, each of which contains 60 mg of diltiazem. Dosages of 30 to 60 mg q 24 hr appear to be effective.

In dogs, diltiazem is often administered alone, or in combination with digoxin, for the treatment of atrial tachycardia and atrial fibrillation (chapter 18). For hemodynamically unstable supraventricular tachyarrhythmia, diltiazem can be administered IV (0.25 mg/kg) over 2 minutes and repeated as needed (maximum total dose, 0.75 mg/kg).[201, 202] In dogs with heart failure, diltiazem offers the advantage of minimally decreasing myocardial contractility. For this reason, some prefer diltiazem to β-blockers for treating dogs with heart failure.[203] Diltiazem's long-term clinical effects in dogs with advanced myocardial or valvular heart disease have not been evaluated. Future studies comparing the antiarrhythmic effects of calcium channel blockers with those of β-adrenergic blocking drugs or other antiarrhythmic agents must consider the long-term effects of these drugs on exercise tolerance and survival.

The reported benefits of diltiazem therapy in cats with hypertrophic cardiomyopathy include reduced heart rates, a positive lusitropic effect (improved diastolic myocardial relaxation), improved diastolic filling, and increased myocardial perfusion.[6, 7, 204] Myocardial relaxation is impaired in humans and cats with HCM, and the amount and distribution of intracellular calcium ions have been implicated in the pathogenesis of this phenomenon. Diltiazem also dilates coronary arteries without producing a pronounced effect on the systemic vasculature.[6, 7] This effect might be clinically important, because cats dying from HCM often show ischemic myocardial lesions in association with abnormal coronary arterioles. Diltiazem could help prevent or delay myocardial cell death and resulting myocardial fibrosis. Decreases in heart rate are due to reduction of calcium-mediated depolarizing currents in the sinoatrial (SA) node, but the SA node remains responsive to increases in circulating catecholamines and sympathetic discharge. For this reason, reductions in heart rate may not be as reliable or as dramatic as those occurring with β-receptor blocking drugs.[7, 199, 204]

Diltiazem has been reported to resolve myocardial hypertrophy in some cats with HCM. One investigator

reported complete resolution of myocardial hypertrophy in 66 percent of cats treated with long-term (≥ 18 months) diltiazem.[7] Many others, including us, have not been able to achieve such remarkable results. Spontaneous resolution of LV hypertrophy sometimes occurs in cats not treated with diltiazem.

Diltiazem has very little negative inotropic effect. This otherwise desirable property may be disadvantageous in treating cats with dynamic outflow tract obstruction. In humans with HCM, diltiazem can increase the severity of dynamic obstruction.[205] Thus, β-blockers appear to be safer and more efficacious in cats with the obstructive form of HCM.[8] There is no consensus of opinion for choosing between β-blockers and calcium channel blockers for those patients with the non-obstructive form of HCM, either in cats or humans.

Adverse reactions to orally administered diltiazem are uncommon. Hypotension is possible with very high doses, particularly when combined with β-blocker or vasodilator drugs. Bradycardia can also occur, particularly in cats concurrently treated with a β-blocker.

REFERENCES

1. Brutsaert DL, Sys SU. Relaxation and diastole of the heart. Physiol Rev 69:1228, 1989
2. Little WC, Downes TR. Clinical evaluation of left ventricular diastolic performance. Prog Cardiovasc Dis 32:273, 1990
3. Brutsaert DL, Sys SU, Gillebert TC. Diastolic failure: Pathophysiology and therapeutic implications. J Am Coll Cardiol 22:318, 1993
4. Gaasch WH. Diagnosis and treatment of heart failure based on left ventricular systolic or diastolic dysfunction. JAMA 271:1278, 1994
5. Bright JM, Golden L, Gompf RE, et al. Evaluation of the calcium channel-blocking agents diltiazem and verapamil for treatment of feline hypertrophic cardiomyopathy. J Vet Intern Med 5:272, 1991
6. Bright JM, Golden AL. Evidence for and against the efficacy of calcium channel blockers for management of hypertrophic cardiomyopathy in cats. *In* Hamlin RL (ed): Vet Clin North Am Small Anim Pract 21:1023, 1991
7. Bonagura JD, Stepien RL, Lehmkuhl LB. Acute effects of esmolol on left ventricular outflow obstruction in cats with hypertrophic cardiomyopathy: A Doppler echocardiographic study; Abstract. J Vet Intern Med 5:123, 1991
8. Fox PR. Evidence for and against the efficacy of beta blockers and aspirin for management of feline cardiomyopathies. *In* Hamlin RL (ed): Vet Clin North Am Small Anim Pract 21:1011, 1991
9. Bonow RO, Rosing DR, Bacharach SL, et al. Effects of verapamil on left ventricular systolic function and diastolic filling in patients with hypertrophic cardiomyopathy. Circulation 64:787, 1981
10. Cheng CP, Freeman GL, Santamore WP. Effect of loading conditions, contractile state and heart rate on early diastolic left ventricular filling in conscious dogs. Circ Res 66:814, 1990
11. Gilligan DM, Chan WL, Joshi J, et al. A double-blind, placebo-controlled crossover trial of nadolol and verapamil in mild and moderately symptomatic hypertrophic cardiomyopathy. J Am Coll Cardiol 21:1672, 1993
12. Levine HJ, Gaasch WH. Clinical recognition and treatment of diastolic dysfunction and heart failure. *In* Gaasch WH, LeWinter MM (eds): Left Ventricular Diastolic Dysfunction and Heart Failure. Philadelphia, Lea & Febiger, 1994, p 445
13. Sisson DD, Thomas WP. Myocardial diseases. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 995
14. Brilla CG, Janicki JS, Weber KT. Comparative effects of lisinopril in rats with genetic hypertension and left ventricular hypertrophy. Circulation 83:1771, 1991
15. Suga H, Sagawa K. Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. Circ Res 35:117, 1974
16. Pion PD, Kittleson MD, Rogers QR, Morris JG. Myocardial failure in cats associated with low plasma taurine: A reversible cardiomyopathy. Science 237:764, 1987
17. Grossman W, Braunwald E, Mann T, et al. Contractile state of the left ventricle in man as evaluated from end-systolic pressure-volume relations. Circulation 56:845, 1977
18. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 56:56, 1975
19. Smith TW, Kelly RA, Stevenson LW, et al. Management of heart failure. *In* Braunwald E (ed): Heart Disease. A Textbook of Cardiovascular Medicine. 5th ed. Philadelphia, WB Saunders, 1997, p 492
20. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in congestive heart failure. N Engl J Med 325:1468, 1991
21. CONSENSUS Trial Study Group. Effect of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Group (CONSENSUS). N Engl J Med 316:1429, 1987
22. SOLVD Investigators: Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 325:293, 1991
23. SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 327:685, 1992
24. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril hydralazine–isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 325:303, 1991
25. Drummond GI, Severson DL. Cyclic nucleotides and cardiac function. Circ Res 44:145, 1979
26. Kittleson MD, Eyster GE, Knowlen GG, et al. Myocardial function in small dogs with chronic mitral regurgitation and severe congestive heart failure. J Am Vet Med Assoc 184:455, 1984
27. Katz AM. Cardiomyopathy of overload. A major determinant of prognosis in congestive heart failure. N Engl J Med 322:100, 1990
28. Nagatsu M, Zile MR, Tsutsui H, et al. Native β-adrenergic support for left ventricular dysfunction in experimental mitral regurgitation normalizes indexes of pump and contractile function. Circulation 89:818, 1994
29. Braunwald E, Welch GH, Sarnoff SJ. Hemodynamic effects of quantitatively varied experimental mitral regurgitation. Circ Res 5:539, 1979

30. Yoran C, Yellin EL, Gabbay S, et al. Mechanism of reduction of mitral regurgitation with vasodilator therapy. Am J Cardiol 43:773, 1979
31. Yoran C, Yellin EL, Becker RM, et al. Dynamic aspects of acute mitral regurgitation: Effects of ventricular volume, pressure and contractility on the effective regurgitant area. Circulation 60:170, 1979
32. Bonagura JD, Darke GG: Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 892
33. Wisenbaugh T, Spann JF, Carabello BA. Differences in myocardial performance and load between patients with similar amounts of chronic aortic versus chronic mitral regurgitation. J Am Coll Cardiol 3:916, 1984
34. Schwartzkopff B, Motz MD, Vogt MD, et al. Heart failure on the basis of hypertension. Circulation 87:IV-66, 1993
35. Kienle RD, Thomas WP, Pion PD. The natural history of canine congenital subaortic stenosis. J Vet Intern Med 8:423, 1994
36. Thomas WP. Therapy of congenital pulmonic stenosis. *In* Bonagura JD (ed): Kirk's Current Veterinary Therapy XII. Small Animal Practice. Philadelphia, WB Saunders, 1995, p 817
37. Monnet E, Orton EC, Gaynor JS, et al. Open resection for subvalvular aortic stenosis in dogs. J Am Vet Med Assoc 209:1255, 1996
38. Weinberg EO, Schoen FJ, George D, et al. Angiotensin-converting enzyme inhibition prolongs survival and modifies the transition to heart failure in rats with pressure overload hypertrophy due to ascending aortic stenosis. Circulation 90:1410, 1994
39. Knight DH. Pathophysiology of heart failure and clinical evaluation of cardiac function. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 844
40. Drobatz KJ, Hackner S, Powell S. Oxygen supplementation. *In* Bonagura JD (ed): Kirk's Current Veterinary Therapy XII. Small Animal Practice. Philadelphia, WB Saunders, 1995, p 175
41. Keene BW, Rush JE. Therapy of heart failure. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 867
42. Unverferth DV, Blanford M. Tolerance to dobutamine after a 72-hour continuous infusion. Am J Med 69:262, 1980
43. Hosgood G. Pharmacologic features and physiologic effects of dopamine. J Am Vet Med Assoc 197:1209, 1990
44. Remme WJ. Inodilator therapy for heart failure: Early, late or not at all? Circulation 87(Suppl IV):IV97, 1993
45. Sisson D. Acquired valvular heart disease in dogs and cats. *In* Bonagura JW (ed): Contemporary Issues in Small Animal Practice. Vol 7: Cardiology. New York, Churchill Livingstone, 1987, p 59
46. Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for Diagnosis. 6th ed. Boston, Little, Brown, 1964
47. O'Grady MR. Does angiotensin-converting enzyme inhibitor therapy delay the onset of congestive heart failure or sudden death in Doberman pinschers with occult dilated cardiomyopathy? Abstract. J Vet Intern Med 11:138, 1997
48. Cody RJ, Covit CB, Schaer GL, et al. Sodium and water balance in chronic congestive heart failure. J Clin Invest 77:1441, 1986
49. Unger T, Ganten D, Lang RE. Effect of converting enzyme inhibitors on tissue-converting enzyme and angiotensin II: Therapeutic implications. Am J Cardiol 59:18D, 1987
50. Haggstrom J, Hansson K, Karlberg BE, et al. Effects of long-term treatment with enalapril or hydralazine on the renin-angiotensin-aldosterone system and fluid balance in dogs with naturally acquired mitral valve regurgitation. Am J Vet Res 57:1645, 1996
51. Knight DH. Efficacy of inotropic support of the failing heart. *In* Hamlin RL (ed): Vet Clinics North Am Small Anim Pract 21:879, 1991
52. The COVE Study Group. Controlled clinical evaluation of enalapril in dogs with heart failure: Results of the Cooperative Veterinary Enalapril Study Group. J Vet Intern Med 9:243, 1995
53. Sica DA, Gehr TW. Diuretic combinations in refractory oedema states. Clin Pharmacokinet 30:229, 1996
54. Kittleson MD, Johnson LE, Olivier NB, et al. Acute hemodynamic effects of hydralazine in dogs with chronic mitral regurgitation. J Am Vet Med Assoc 187:258, 1985
55. Spokas EG, Wang H. Regional blood flow and cardiac responses to hydralazine. J Pharm Exp Ther 212:294, 1980
56. Conti CR. Use of calcium antagonists to treat heart failure. Clin Cardiol 17:101, 1994
57. Packer M, O'Connor CM, Ghali JK. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. N Engl J Med 335:1107, 1996
58. Yamanaka K, Suzuki M, Ishiko J. Antihypertensive effects of amlodipine, a new calcium antagonist. Nippon Yakurigaku Zasshi 97:115, 1991
59. Rich S, Kaufman E, Levy PS. The effect of high doses of calcium channel blockers on survival in primary pulmonary hypertension. N Engl J Med 327:76, 1992
60. Birchard SJ, Bonagura JD, Fingland RB. Results of ligation of patent ductus arteriosus in dogs: 201 cases (1969–1988). J Am Vet Med Assoc 196:2011, 1990
61. Miller MW, Bonagura JD, Meurs KM. Percutaneous catheter occlusion of patent ductus arteriosus. Proceedings of the 13th Annual Veterinary Medical Forum, 1995, p 308
62. Sisson D, Thomas WP. Endocarditis of the aortic valve. J Am Vet Med Assoc 184:570, 1984
63. Snyder PS. Blinded trial of amlodipine in cats with hypertension; Abstract. J Vet Intern Med 11:139, 1997
64. Stopher DA, Beresford AP, Macrae PV, et al. The metabolism and pharmacokinetics of amlodipine in humans and animals. J Cardiovasc Pharmacol 12 Suppl 7:S55, 1988
65. Withering W. An account of the foxglove and some of its medical uses, with practical remarks on dropsy, and other diseases. *In* Willis FA, Keys TE (eds): Classics of Cardiology. New York, Henry Schuman, 1941
66. Dobbs SM, Kenyon WI, Dobbs RJ. Maintenance digoxin after an episode of heart failure: Placebo-controlled trial in outpatients. Br Med J 1:749, 1977
67. Kleiman JH, Ingels NB, Daughters G. Left ventricular dynamics during long-term digoxin treatment in patients with stable coronary artery disease. Am J Cardiol 41:937, 1978
68. Arnold SB, Byrd RC, Meister W, et al. Long-term digitalis therapy improves left ventricular function in heart failure. N Engl J Med 303:1443, 1980
69. Mulrow CD, Feussner JR, Velez R. Reevaluation of digitalis efficacy. Ann Intern Med 101:113, 1984
70. Uretsky BF, Young JB, Shahidi FE. Randomized study

assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: Results of the PROVED trial. J Am Coll Cardiol 22:955, 1993
71. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting enzyme inhibitors. N Engl J Med 329:1, 1993
72. McHaffie D, Purcell H, Mitchell-Heggs P, Guz A. The clinical value of digoxin in patients with heart failure and sinus rhythm. Q J Med 188:401, 1978
73. Davidson C, Gibson D. Clinical significance of positive inotropic action of digoxin in patients with left ventricular disease. Br Heart J 35:970, 1973
74. The Digoxin Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 336:525, 1997
75. Kittleson MD, Eyster GE, Knowlen GG, et al. Efficacy of digoxin administration in dogs with idiopathic congestive cardiomyopathy. J Am Vet Med Assoc 186:162, 1985
76. Hougen TJ, Smith TW. Inhibition of myocardial monovalent cation active transport by subtoxic doses of ouabain in the dog. Circ Res 42:856, 1978
77. Caprio A, Farah A. The effect of the ionic milieu on the response of rabbit cardiac muscle to ouabain. J Pharm Exp Ther 155:403, 1967
78. Mason DT, Zelia R, Amsterdam EA (eds). Unified concept of the mechanism of action of digitalis: Influence of ventricular function and cardiac disease on hemodynamic response to fundamental contractile effect. *In* Marks BH, Weissler AM (eds): Basic and Clinical Pharmacology of Digitalis. Springfield, IL, CV Mosby, 1972, p 283
79. Chidsey CA. Calcium Metabolism in the Normal and Failing Heart. New York, HP Publishing Co, 1974
80. Ferrier GR, Moe GK. Effect of calcium on acetylstrophanthidin-induced transient depolarization in canine Purkinje tissue. Circ Res 33:508, 1973
81. Moe GK, Farah AE. Digitalis and allied cardiac glycosides. *In* Goodman LS, Gilman A (eds): Pharmacological Basis of Therapeutics. 4th ed. New York, Macmillan, 1970, p 677
82. Krum H, Bigger JT Jr, Goldsmith RL, et al. Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. J Am Coll Cardiol 25:289, 1995
83. Baggot JD, Davis LE. Plasma protein binding of digitoxin and digoxin in several mammalian species. Res Vet Sci 15:81, 1973
84. Breznock EM. Application of canine plasma kinetics of digoxin and digitoxin to therapeutic digitalization in the dog. J Am Vet Med Assoc 34:993, 1973
85. Weidler DFJ, Jazllad NS, Movahhed HS, et al. Pharmacokinetics of digoxin in the cat and comparisons with man and the dog. Res Comm Chem Pathol Pharm 19:57, 1987
86. Doherty JE. Pharmacokinetics and their clinical implications. Ann Intern Med 79:299, 1973
87. De Rick A, Balpaire FM, Bogaert MG, et al. Plasma concentrations of digoxin and digitoxin during digitalization of healthy dogs and dogs with cardiac failure. Am J Vet Res 39:811, 1978
88. Bolton GRP. Pharmacokinetics of digoxin in the cat. Preliminary report. Personal communication.
89. Erichsen DF, Harris SG, Upson DW. Plasma levels of digoxin in the cat: Some clinical applications. J Am Anim Hosp Assoc 14:734, 1978
90. Hamlin RL. Basis for selection of a cardiac glycoside for dogs. Proceedings of the First Symposium on Veterinary Pharmacology and Therapeutics, Baton Rouge, LA, 1978
91. Kittleson MD. Drugs used in the management of heart failure. *In* Kirk RW (ed): Current Veterinary Therapy. Vol VIII. Philadelphia, WB Saunders, 1983, p 285
92. Pedersoli WM. Serum digoxin concentrations in healthy dogs treated without a loading dose. J Vet Pharm Ther 1:279, 1978
93. DeMots H, McAnulty JH, Porter GA, et al. Effects of rapid and slow infusion of ouabain on systemic and coronary vascular resistance in patients not in clinical heart failure. Circulation 52:77, 1975
94. Gierke KD, Perrier D, Mayersohn M, Marcus EL. Digoxin disposition kinetics in dogs before and during azotemia. J Pharm Exp Ther 205:459, 1978
95. Bonagura JD, Ware WA. Atrial fibrillation in the dog: Clinical findings in 81 cases. J Am Anim Hosp Assoc 22:111, 1986
96. Smith TW. Digitalis. III. N Engl J Med 289:1063, 1973
97. Fox PR. Feline myocardial diseases. *In* Kirk RW (ed): Current Veterinary Therapy. Vol VIII. Philadelphia, WB Saunders, 1983, p 387
98. Bigger JT. The quinidine-digoxin interaction. Mod Concepts Cardiovasc Dis 51:73, 1982
99. Warner NJ, Barnard JT, Uhl JT, et al. Digoxin, quinidine and monovalent cation transport. Circulation 66:57, 1982
100. Klein HO, Land R, Weiss E, et al. The influence of verapamil on serum digoxin concentration. Circulation 65:998, 1982
101. Zatuchni J. Verapamil-digoxin concentration. Am Heart J 108:412, 1980
102. Breznock EM. Effects of phenobarbital on digitoxin and digoxin elimination in the dog. Am J Vet Res 36:371, 1975
103. Pedersoli WM. Serum digoxin concentration in dogs before and after concomitant treatment with chloramphenicol. J Am Anim Hosp Assoc 16:839, 1980
104. Gross DR, Hamlin RL, Pipers FS. Response of P-Q intervals to digitalis glycosides in the dog. J Am Vet Med Assoc 162:888, 1973
105. Smith TW. Digitalis toxicity: Epidemiology and clinical use of serum concentration measurements. Am J Med 58:470, 1975
106. Borison HL, Wang SC. Physiology and pharmacology of vomiting. Pharmacol Rev 5:193, 1953
107. Gillis RA: Digitalis: A neuroexcitatory drug. Circulation 52:739, 1975
108. Karagueuzian HS, Katzung BG. Relative inotropic and arrhythmogenic effects of five cardiac steroids in ventricular myocardium: Oscillatory afterpotentials and the role of endogenous catecholamines. J Pharm Exp Ther 218:348, 1981
109. Citrin D, Stevenson IH, O'Malley K. Massive digoxin overdose: Observations on hyperkalemia and plasma digoxin levels. Scott Med J 17:275, 1972
110. Dreifus LS, McKnight EH, Katz M, Likoff W. Digitalis intolerance. Geriatrics 18:494, 1963
111. Peon J, Ferrier GR, Moe GK. The relationship of excitability to conduction velocity in canine Purkinje tissue. Circ Res 43:125, 1978
112. Rall TW, Schleifer LS. Drugs effective in the therapy of the epilepsies. *In* Gilman AG, Goodman LS, Gilman A (eds): The Pharmacological Basis of Therapeutics. 6th ed. New York, Macmillan, 1980, p 539
113. Sanders JE, Yeary RA. Serum concentrations of orally

administered diphenylhydantoin in dogs. J Am Vet Assoc 172:153, 1978
114. Caldwell JH, Bush CA, Greenberger NJ. Interruption of the enterohepatic circulation of digitoxin by cholestyramine. Effect on metabolic disposition of tritium-labeled digitoxin and cardiac systolic intervals in man. J Clin Invest 50:2638, 1971
115. Smith TW, Butler VP, Haber E, et al. Treatment of life-threatening digitalis intoxication with digoxin-specific antibody fragments. N Engl J Med 307:1357, 1982
116. Lindemann JP, Watanabe AM. Mechanisms of adrenergic and cholinergic regulation of myocardial contractility. *In* Sperekalakis N (ed): Physiology and Pathophysiology of the Heart. 3rd ed. Boston, Kluwer Academic Publishers, 1995, p 467
117. Adams HR. New perspectives in cardiopulmonary therapeutics: Receptor-selective adrenergic drugs. J Am Vet Med Assoc 85:966, 1984
118. Maekawa K, Liang H, Hood WB. Comparison of dobutamine and dopamine in acute myocardial infarction. Circulation 67:750, 1983
119. Murphy PJ, Williams TL, Kau DKL. Disposition of dobutamine in the dog. J Pharm Exp Ther 199:423, 1976
120. McNay JL, McDonald RH, Goldgern LI. Direct renal vasodilatation produced by dopamine in the dog. Circ Res 16:510, 1965
121. Loeb HS, Bredzakis J, Gunner RM. Superiority of dobutamine over dopamine for augmentation of cardiac output in patients with chronic low output cardiac failure. Circulation 5:375, 1977
122. Robie NW, Goldberg LI. Comparative systemic and regional hemodynamic effects of dopamine and dobutamine. Am Heart J 90:340, 1975
123. Vatner SF, McRitchie J, Braunwald E. Effects of dobutamine on left ventricular performance, coronary dynamics, and distribution of cardiac output in conscious dogs. J Clin Invest 53:1265, 1974
124. Unverferth DV, Magorian RD, Lewis RP, et al. Long-term benefit of dobutamine in patients with congestive cardiomyopathy. Am Heart J 100:622, 1980
125. Sacher HL, Sacher ML, Landau SW, et al. Outpatient dobutamine therapy: The rhyme and the riddle. J Clin Pharmacol 32:141, 1992
126. Mancini D, LeJemetel T, Sonnenblick E. Intravenous use of amrinone for the treatment of the failing heart. Am J Cardiol 56:8B, 1985
127. Ludmer PL, Wright RF, Arnold JMO, et al. Separation of the direct myocardial and vasodilator actions of milrinone administered by an intracoronary infusion technique. Circulation 73:130, 1986
128. A Summary of Laboratory and Clinical Data on Inocor (brand of amrinone). Rensselaer, NY, Sterling Winthrop Research Institute, 1980
129. Treadway G. Clinical safety of intravenous amrinone. A review. Am J Cardiol 56:39B, 1985
130. Alousi AA, Canter JM, Montenaro MJ, et al. Cardiotonic activity of milrinone, a new and potent cardiac bipyridine, on the normal and failing heart of experimental animals. J Cardiovasc Pharm 5:792, 1983
131. Kittleson MD, Pipers FS, Knauer KW, et al. Echocardiographic and clinical effect of milrinone in dogs with myocardial failure. Am J Vet Res 46:1659, 1985
132. Kittleson MD, Johnson LE, Pion PD. The acute hemodynamic effects of milrinone in dogs with severe idiopathic myocardial failure. J Vet Intern Med 1:127, 1987
133. Jackson EK. Diuretics and other agents employed in the mobilization of edema fluid. *In* Hardman JG, Limbird L (eds): Goodman & Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, McGraw-Hill Book Company, 1996
134. Brater DC. Disposition and response to bumetanide and furosemide. Am J Cardiol 57:20A, 1986
135. Haas M. The Na-K-Cl cotransporters. Am J Physiol 267:C869, 1994
136. Raftery EB. Hemodynamic effects of diuretics in heart failure. Br Heart J 72:44, 1994
137. Cody RJ, Kubo SH, Pickworth KK. Diuretic treatment for the sodium retention of congestive heart failure. Arch Intern Med 154:1905, 1994
138. Ellison DH. The physiologic basis of diuretic synergism: Its role in treating diuretic resistance. Ann Intern Med 114:886, 1991
139. Gamba G, Saltzberg SN, Lambardi M, et al. Primary structure and functional expression of a cDNA encoding the thiazide-sensitive electroneutral sodium-chloride cotransporter. Proc Natl Acad Sci 90:2749, 1993
140. Brater DC, Their SO. Renal Disorders. New York, Macmillan, 1978
141. Karim A, Kook C, Zitzewitz DJ, et al. Species differences in the metabolism and disposition of spironolactone. Drug Metab Dispos 4:547, 1976
142. Wang W, McClain JM, Zucker IH. Aldosterone reduces baroreceptor discharge in the dog. Hypertension 19:270, 1992
143. Crosley AP, Ronquillo LM, Strickland WH, et al. Triamterene, a new natriuretic agent. Ann Intern Med 56:241, 1962
144. Burges RA, Dodd MG, Gardiner DG. Pharmacologic profile of amlodipine. Am J Cardiol 64:101, 1989
145. Packer M, O'Connor CM, Ghali JK. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. N Engl J Med 335:1107, 1996
146. Yamanaka K, Suzuki M, Ishiko J. Antihypertensive effects of amlodipine, a new calcium antagonist. Nippon Yakurigaku Zasshi 97:115, 1991
147. Greenwald JE. Modulation of prostaglandin biosynthesis: Proposed mechanism of action of hydralazine. Dissertation, Ohio State University, Akron, OH, 1981
148. Spokas EG, Wang H. Regional blood flow and cardiac responses to hydralazine. J Pharm Exp Ther 212:294, 1980
149. Cogan JJ, Humphreys MH, Carlson CJ. Acute vasodilator therapy increases renal clearance of digoxin in patients with congestive heart failure. Circulation 64:973, 1981
150. Kittleson MD, Johnson LE, Olivier NG. Acute hemodynamic effects of hydralazine in dogs with chronic mitral regurgitation. J Am Vet Med Assoc 187:258, 1985
151. Kittleson MD, Hamlin RL. Hydralazine pharmacodynamics in the dog. Am J Vet Res 44:1501, 1983
152. Koch-Weser J: Hydralazine. N Engl J Med 295:320, 1976
153. Kittleson MD, Eyster GE, Olivier NB, et al. Oral hydralazine therapy for chronic mitral regurgitation in the dog. J Am Vet Med Assoc 182:1205, 1983
154. Lowenstein J, Steele JM. Prazosin. Am Heart J 95:262, 1978
155. Packer M, Meller J, Gorlin R, et al. Hemodynamic and clinical tachyphylaxis to prazosin-mediated afterload reduction in severe chronic congestive heart failure. Circulation 59:531, 1979
156. Smith RD, Tessman DK, Kaplan HR. Acute tolerance to prazosin in conscious hypertensive rats: Involvement of the renin-angiotensin system. J Pharm Exp Ther 217:397, 1981
157. Awan NA, Miller RR, DeMaria AN, et al. Efficacy of ambulatory systemic vasodilator therapy with oral pra-

zosin in chronic refractory heart failure. Circulation 56:346, 1977
158. Harrison DG, Bates JN. The nitrovasodilators: New ideas about old drugs. Circulation 87:1461, 1993
159. Hamlin RL. Evidence for or against clinical efficacy of preload reducers. *In* Hamlin RL (ed): Vet Clin North Am Small Anim Pract 21:931, 1991
160. Kittleson MD. Management of heart failure. Concepts, strategies, and drug pharmacology. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 171
161. Jugdutt BI, Khan MI. Effect of prolonged nitrate therapy on left ventricular remodeling after canine acute myocardial infarction. Circulation 89:2297, 1994
162. McDonald KM, Francis GS, Matthews J, et al. Long-term oral nitrate therapy prevents chronic ventricular remodeling in the dog. J Am Coll Cardiol 21:514, 1993
163. Jugdutt BI, Khan MI, Jugdutt SJ, et al. Impact of left ventricular unloading after late reperfusion of canine anterior myocardial infarction on remodeling and function using isosorbide-5-mononitrate. Circulation 92:926, 1995
164. Committee on Evaluation and Management of Heart Failure. Guidelines for the evaluation and treatment of heart failure. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 92:2764, 1995
165. Fox PR, Sisson DD. Angiotensin-converting enzyme inhibitors. *In* Bonagura JD (ed): Kirk's Current Veterinary Therapy XII. Small Animal Practice. Philadelphia, WB Saunders, 1995, p 786
166. The IMPROVE Study Investigators. Clinical effects of enalapril maleate in dogs with naturally acquired heart failure: Results of the invasive multicenter prospective veterinary evaluation of enalapril. J Vet Intern Med 9:234, 1995
167. Hofmann S, Kersten U. The effectiveness and tolerance of ramipril in comparison to captopril for heart failure in dogs. DTW Dtsch Tierarztl Wochenschr 103:159, 1996
168. Morisse B, Kersten U. Treatment of heart failure in dogs with ACE inhibitors: Comparison of quinapril and captopril. Tierarztl Prax 23:489, 1995
169. Pouchelon JL, Benazepril Veterinary Investigators. Treatment of heart failure in dogs with benazepril—Results of European double-blind placebo-controlled study; Abstract. J Vet Intern Med 10:163, 1996
170. Kelly JG, O'Malley K. Clinical pharmacokinetics of the newer ACE inhibitors. A review. Clin Pharmacokinet 19:177, 1990
171. Eckert HG, Badian MJ, Gantz D, et al. Pharmacokinetics and biotransformation of ramipril in rat, dog, and man. Arzneimittelforschung 34:1435, 1984
172. Unger T, Ganten D, Lang RE. Effect of converting enzyme inhibition on tissue converting enzyme and angiotensin II: Therapeutic implications. Am J Cardiol 59:18D, 1987
173. Allen AA, Wilke LE, Fettman MJ. Captopril and enalapril: Angiotensin-converting enzyme inhibitors. J Am Vet Med Assoc 190:94, 1987
174. Kittleson MD. The acute hemodynamic effects of captopril in dogs with heart failure. J Vet Pharmacol Ther 16:1, 1993
175. Hamlin RL, Nakayama T. Comparison of some pharmacokinetic parameters of 5 angiotensin-converting enzyme inhibitors (ACEI's) in normal beagle hounds. J Vet Intern Med (in press)
176. Gross DM, Sweet CS, Ulm EH, et al. Effect of N-[(s)-1-carboxy-3-phenylpropyl]-L-Ala-L-Pro and its ethyl ester (MK-421) on angiotensin-converting enzyme in vitro and angiotensin I pressor responses in vivo. J Pharmacol Exp Ther 216:552, 1981
177. Tocco DJ, deLuna FA, Duncan AE, et al. The physiological disposition and metabolism of enalapril maleate in laboratory animals. Drug Metab Dispos 10:15, 1982
178. Ettinger SJ. ACE inhibitors—why, when, and why not? Proceedings of the 15th Annual Veterinary Medical Forum, 1997, p 194
179. Gomez HJ, Cirillo VJ, Moncloa F. The clinical pharmacology of lisinopril. J Cardiovasc Pharmacol 9:S27, 1987
180. Oda M, Ino Y, Suzuki K, et al. Angiotensin-converting enzyme inhibitory activity of MK-0521 in vivo and antihypertensive effect of its oral administration on blood pressure and effect on the renin-angiotensin system in 2-kidney Goldblatt hypertensive dogs. Nippon Yakurigaku Zasshi 93:225, 1989
181. King JN, Mauron C, Kaiser G. Pharmacokinetics of the active metabolite of benazepril, benazeprilat, and inhibition of plasma angiotensin-converting enzyme activity after single repeated administration to dogs. Am J Vet Res 56:1620, 1995
182. King JN, Humbert-Droz E, Maurer M. Pharmacokinetics of benazepril and inhibition of plasma ACE activity in cats; Abstract. J Vet Intern Med 10:163, 1996
183. Longhofer SL, Ericsson GF, Cifelli S, et al. Renal function in heart failure dogs receiving furosemide and enalapril maleate; Abstract. J Vet Intern Med 7:123, 1993
184. Gottlieb SS, Weir MR. Renal effects of angiotensin-converting enzyme inhibition in congestive heart failure. Am J Cardiol 66:14D, 1990
185. Ware WA. Current uses and hazards of beta-blockers. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI. Small Animal Practice. Philadelphia, WB Saunders, 1992, p 676
186. Bristow MR. Changes in myocardial and vascular receptors in heart failure. J Am Coll Cardiol 22:61A, 1993
187. Floras JS. Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure. J Am Coll Cardiol 22:72A, 1993
188. Waagstein F, Caidahl K, Wallentin I, et al. Long-term β-blockade in dilated cardiomyopathy. Effects of short- and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. Circulation 80:551, 1989
189. CIBIS Investigators and Committees. A randomized trial of β-blockade in heart failure: The cardiac insufficiency bisoprolol study (CIBIS). Circulation 90:1765, 1994
190. Eichhorn EJ. The paradox of beta-adrenergic blockade for the management of congestive heart failure. Am J Med 92:527, 1992
191. Bristow MR. Pathophysiologic and pharmacologic rationales for clinical management of chronic heart failure with beta-blocking agents. Am J Cardiol 71:12C, 1993
192. Quinones M, Dyer DC, Ware WA, et al. Pharmacokinetics of atenolol in clinically normal cats. Am J Vet Res 57:1050, 1996
193. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation 94:2807, 1997
194. Shimoyama H, Sabbah HN, Rosman H, et al. Effect of β-blockade on left atrial contribution to ventricular filling in dogs with moderate heart failure. Am Heart J 131:772, 1996

195. O'Connor CM, Belkin RN, Carson PE, et al. Effect of amlodipine on mode of death in severe chronic heart failure: the PRAISE trial; Abstract. Circulation 92 (Suppl I:I–143, 1995
196. Ruschitzka FT, Luscher TF. Is there a rationale for combining angiotensin-converting enzyme inhibitors and calcium antagonists in cardiovascular disease? Am Heart J 134:S31, 1997
197. Piepho RW, Bloedow DC, Lacz JP, et al. Pharmacokinetics of diltiazem in selected animal species and human beings. Am J Cardiol 49:525, 1982
198. Johnson LM, Atkins CE, Keene BW, et al. Pharmacokinetic and pharmacodynamic properties of conventional and CD-formulated diltiazem in cats. J Vet Intern Med 10:316, 1996
199. Pion PD. Current uses and hazards of calcium channel blocking agents. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI. Small Animal Practice. Philadelphia, WB Saunders, 1992, p 684
200. Atkins CE. Feline hypertrophic cardiomyopathy. Am Anim Hosp Assoc Scientific Proceedings, 1997, p 3
201. Russel LC, Rush JE. Cardiac arrhythmias in systemic disease. *In* Bonagura JD (ed): Kirk's Current Veterinary Therapy XII. Small Animal Practice. Philadelphia, WB Saunders, 1995, p 161
202. Fujiki A, Mizumaki K, Tani M. Effects of diltiazem on concealed atrioventricular nodal conduction in relation to ventricular response during atrial fibrillation in anesthetized dogs. Am Heart J 125:1284, 1993
203. Salerno DM, Dias VC, Kleiger RE. Efficacy and safety of intravenous diltiazem for treatment of atrial fibrillation and atrial flutter. Am J Cardiol 63:1046, 1989
204. Bright JM. Update: Diltiazem therapy of feline hypertrophic cardiomyopathy. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI. Small Animal Practice. Philadelphia, WB Saunders, 1992, p 766
205. Betocchi S, Piscione F, Losi MA, et al. Effects of diltiazem on left ventricular systolic and diastolic function in hypertrophic cardiomyopathy. Am J Cardiol 78:45, 1996

13

Pulmonary Edema

WENDY A. WARE
JOHN D. BONAGURA

Pulmonary edema is the abnormal accumulation of extravascular pulmonary fluid. Pulmonary edema develops when fluid movement into the lung exceeds the capacity of lymphatic drainage.[1,2] It can cause disability and death by disrupting gas exchange and lung mechanics. The focus of this chapter is cardiogenic pulmonary edema, although other causes are also briefly discussed.

THE NORMAL PULMONARY CIRCULATION

ALVEOLAR-CAPILLARY STRUCTURE

Pulmonary alveoli are richly supplied with capillaries (Fig. 13–1). The capillary endothelial cells interdigitate extensively, and relatively weak ("loose") intercellular junctions are formed where cells overlap.[3] Consequently, communication between pulmonary capillaries and the interstitial space is facilitated. While movement of proteins across this membrane is somewhat restricted, the pulmonary capillaries are more permeable to proteins than are the systemic capillaries.[1,4]

Each capillary is surrounded by an interstitial space of varying thickness. On one side of the capillary this space is very narrow and the capillary wall closely abuts the alveolar epithelium; this juncture is believed to be the major surface for pulmonary gas exchange. Areas of thicker interstitial space contain connective tissue fibrils, fibroblasts, and macrophages.[3] Fluid filtered from the capillaries first accumulates in these areas, which are continuous with the larger, more compliant spaces around terminal bronchioles, small arteries, and veins. Lymphatic drainage occurs from the interstitium of these latter structures.[1-3] There are no lymphatic channels in the alveolar-capillary interstitium.

The alveolar wall is lined primarily with large squamous cells (Type I) and smaller numbers of granular pneumocytes (Type II). In contrast to the capillary endothelium, alveolar epithelial cells are fused together to form "tight" intercellular junctions. These are thought to help protect the alveolus from flooding. Surfactant, a hydrophobic lipoprotein that lines the alveoli, acts to maintain alveolar stability by minimizing surface tension, and it helps impede the onset of alveolar flooding.[3,5,6]

CAPILLARY–INTERSTITIAL FLUID EXCHANGE

Classically, the Starling equation has been used to describe the net fluid flow out of the capillary into the interstitial space in terms of the balance between hydrostatic and osmotic forces, modified by certain membrane characteristics. This flow (Q) is determined by the difference between capil-

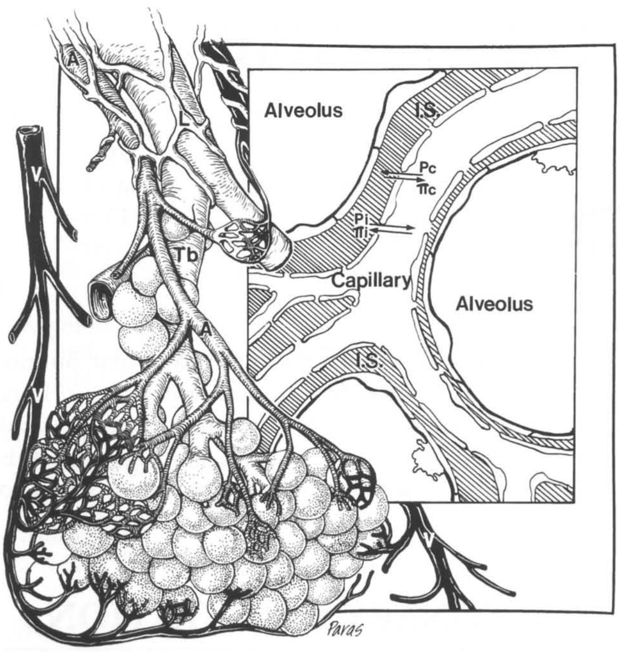


FIGURE 13–1

A respiratory unit. The arteriole branches into capillary plexus surrounding alveoli. Starling's forces controlling fluid movement into or out of the capillary are indicated. P_c, capillary hydrostatic pressure; π_c, capillary colloid osmotic pressure; P_i interstitial hydrostatic pressure; π_i, interstitial colloid osmotic pressure; A, arteriole; V, venule; L, lymphatic vessel; Tb, terminal bronchiole; I.S., interstitial space.

lary (P_c) and interstitial (P_i) hydrostatic pressures and the capillary (π_c) and interstitial (π_i) colloid osmotic pressure gradient. Thus,

$$Q = K[(P_c - P_i) - \sigma (\pi_c - \pi_i)]$$

where K is the capillary filtration coefficient (hydraulic conductivity times surface area of the capillary wall) and σ is the reflection coefficient, which defines the permeability of the microvascular wall to proteins.[1, 2, 7] This relationship shows that fluid movement into the interstitium results from high capillary hydrostatic pressure, low capillary osmotic pressure (rarely a cause), or increased capillary permeability. However, experiments have shown that the formation of pulmonary edema cannot be neatly grouped into these categories.[8–11]

PULMONARY CIRCULATION AND LYMPHATICS

Overall pulmonary capillary hydrostatic pressure is low compared with the systemic circulation. Within the lung, gravitational influences result in greater hydrostatic pressure ventrally. A major portion of the pulmonary arterial-to-venous pressure drop occurs in the alveolar wall capillary rather than in the arteriole.[12] Pulmonary interstitial pressure also is lower than systemic pressure and is well below atmospheric pressure.

The pulmonary lymphatics play an important role in removing fluid from the interstitial space. Fluid moves from alveolar-capillary areas toward adjacent perivascular and peribronchial interstitium where lymphatics are located.[1, 12] Lymph flows toward the bronchial and hilar lymph nodes, finally returning to the venous circulation. Lymphatic flow results from intrinsic lymph vessel wall contractions as well as the pumping action caused by fluctuating pleural pressure and vascular pulsations.[3, 4, 13] Valves within the lymphatics maintain unidirectional flow.

When the capacity for lymphatic drainage is exceeded, interstitial fluid accumulates. However, there is a tremendous capacity for lymphatic diameter and flow to increase in response to greater interstitial fluid accumulation. Lymphatic flow in normal dogs has been estimated at 4 to 20 ml/hr.[1, 14, 15] With chronic elevations in left atrial pressure, the lymphatic system hypertrophies. Increases in lymphatic flow of 300 to 2800 percent over control have been demonstrated in a canine model of chronic congestive heart failure.[3, 14] Free interstitial fluid may also drain into the pleural space or flow along bronchovascular connective tissue into the mediastinum to be removed by mediastinal lymphatics.[12, 16]

Factors tending to protect against overt pulmonary edema include the fluid clearance pathways (lymphatic vessels, pleural space, mediastinum), the normally low rates of liquid filtration and protein leak, and the high plasma protein concentration.[4, 16] Since lymphatic walls are also very permeable, accumulated interstitial proteins are removed along with fluid. Lymphatic removal of interstitial proteins and/or increasing interstitial hydrostatic pressure helps retard the formation of further edema.[4]

CAUSES OF PULMONARY EDEMA

Pulmonary edema has traditionally been categorized as being caused by either increased pulmonary capillary hydrostatic pressure or increased alveolar-capillary membrane permeability. It is now apparent that this classification is somewhat inaccurate and misleading. Damage to the alveolar-capillary membrane occurs secondary to increased capillary hydrostatic pressures, and this damage increases membrane permeability to plasma proteins.[8–10] Furthermore, pulmonary insults that were previously thought to cause edema only by increasing alveolar-capillary membrane permeability also often involve increased capillary pressures as well.[8] With this in mind, an overview of certain clinical causes of pulmonary edema is presented next.

CARDIOGENIC PULMONARY EDEMA

Elevated pulmonary capillary pressure secondary to left-sided heart failure often initiates pulmonary edema. Common causes of this in dogs and cats include various cardiomyopathies (especially hypertrophic cardiomyopathy in cats and dilated cardiomyopathy in dogs) and volume overloads caused by mitral and aortic valve insufficiency and patent ductus arteriosus. Acute left ventricular dysfunction from other causes, as well as severe arrhythmias, can also result in cardiogenic pulmonary edema.[17, 18] Rarely, obstructive lesions of the left atrium (e.g., neoplasia or thrombus), a major pulmonary vein, or mitral valve orifice (e.g., mitral valve stenosis) lead to this so-called "high-pressure" pulmonary edema. Excessive pulmonary blood flow resulting from a congenital left-to-right cardiac shunt (e.g., patent ductus arteriosus), anemia, or exercise can promote pulmonary edema. Clinical edema is more likely to occur when marked volume overloading occurs in the presence of left ventricular diastolic dysfunction.[2]

Overzealous intravenous fluid administration (greater than 100 ml/kg/hr in normal dogs) can cause or exacerbate pulmonary edema by increasing capillary hydrostatic pressure and diluting serum proteins. Systemic venous hypertension has experimentally been shown to contribute to increased lung water and edema, probably by inducing bronchial venous hypertension and/or impeding lymphatic drainage.[3, 19]

The amount of edema formed depends in part on the rate of rise of intravascular pressures and vascular permeability.[1, 20] Normal dogs subjected to acute increases in left atrial pressure above 23 mmHg develop lung edema. Conversely, pressure can be chronically elevated to 40 to 45 mmHg without development of significant edema because of gradually increasing lymphatic capacity.[4] Such chronic elevations can be associated with pulmonary hypertension and secondary right ventricular failure.

Increases in capillary pressure cause ultrastructural distortion and injury to capillary endothelium, alveolar epithelium, or all layers of the membrane.[20–22] "Stretching" of the loose junctions between endothelial cells allows fluid and protein passage during high perfusion pressure. These junctions can return to a more normal appearance once the pressure is relieved, which may explain the minimal endothelial injury found in some reports. In contrast, marked disruption of alveolar epithelial cells was seen in areas of greatest alveolar and interstitial edema.[20–22] Epithelial "tight" junctions and fewer intercellular junctions per unit area compared with endothelium presumably cause higher resistance to pericellular fluid movement and damage from sheer pressures caused by alveolar interstitial edema.[9–11] Secondarily, exposure of basement membrane can attract and activate platelets and neutrophils, leading to intercurrent increases of vascular permeability that further enhance edema formation.[21, 22] There is evidence that platelet degranulation products also may contribute to pulmonary edema formation in congestive heart failure.[23] Metabolic as well as structural changes are also thought to occur in alveolar epithelial cells in response to edema formation.[9, 10]

PRIMARY ALVEOLAR-CAPILLARY MEMBRANE INJURY

Pulmonary edema resulting from primary damage to the alveolar-capillary membrane ("high-permeability" edema) is sometimes called the adult respiratory distress syndrome (ARDS) or "shock lung" in people. Alveolar-capillary membrane injury can develop following a wide variety of pulmonary insults, including inhalation of toxic gases, smoke, or gastric secretions; acute pulmonary infections; endotoxic, cardiogenic, or hypovolemic shock; gram-negative septicemia; pancreatitis; trauma; pulmonary microemboli; anaphylaxis; immune complex disease; exposure to toxic substances (including organophosphates and herbicides [e.g., paraquat], alpha-naphthylthiourea [ANTU], insect and snake venoms); uremia; or prolonged exposure to high concentrations of O_2.[2, 12, 24–32] There is strong experimental and clinical evidence indicating that polymorphonuclear leukocytes and various chemotactic agents and cytokines initiate and perpetuate injury leading to high-permeability pulmonary edema.[3, 29, 33, 34] The pathogenesis of permeability edema includes direct pulmonary damage and indirect injury mediated by vasoactive components of the clotting cascade, leukotrienes, lysosomal enzymes, cytokines released from monocytic cells (such as various interleukins and tumor necrosis factor), platelet factors, and oxygen-free radicals.[3, 12, 30, 35–44b]

Increased microvascular pressure also plays a role in high-permeability lung edema.[45, 46] Capillary pressure increases during inflammation. Some inflammatory mediators have even been shown to induce a purely hydrostatic edema without measurable change in capillary permeability, whereas others increase both capillary pressure and permeability. Capillary pressure may rise (e.g., with increased postcapillary vascular resistance) even with decreased or unchanged pulmonary artery occlusion pressures.[8] These pressure changes emphasize the dilemma of volume infusion in the management of permeability lung edema. Since many of the underlying conditions (e.g., septic shock) are usually treated with volume expansion, the potential to increase flow to affected lung lobes and further promote edema formation must be appreciated. The protein exudation associated with high-permeability

edema inhibits resorption of fluid from the interstitium. Moreover, alveolar flooding inhibits the function of lung surfactant complex and can secondarily increase microvascular permeability.[47]

A high-protein coating in the alveolus reduces gas exchange and alveolar compliance.[2] The protein content of edema fluid caused by primary alveolar-capillary membrane damage can be 70 to 100 percent of plasma protein concentration; protein concentrations of cardiogenic edema have been reported at 40 to 50 percent of plasma.[12, 15, 48, 49]

OTHER CAUSES OF PULMONARY EDEMA (NONCARDIOGENIC PULMONARY EDEMA)

Pulmonary edema can be neurogenic in origin, resulting from head trauma, seizures, intoxicants (e.g., organophosphate and chlorinated hydrocarbons), other central nervous system lesions, or electrocution. A combination of hemodynamic and permeability changes interacts to cause neurogenic edema.[3, 12, 50–53] Acute sympathetic overactivity causes decreased capacitance of the pulmonary bed, shifts blood volume from the systemic to the pulmonic circulation, and markedly increases pulmonary vascular pressures. However, pulmonary capillary pressure is only transiently raised. In addition to mechanical capillary-alveolar membrane injury, neural stimulation itself causes some degree of altered permeability.[3, 53, 54]

A review of 26 cases of noncardiogenic pulmonary edema in 23 dogs and 3 cats revealed associated causes to include airway obstruction (8), cranial trauma (7), electric shock (7), and seizures (4). Nineteen of the 26 were less than 1 year of age. Radiographic patterns compatible with pulmonary edema were asymmetric in 83 percent of the animals.[53a] Lung injury leading to the respiratory distress syndrome in young Dalmatian dogs was characterized by pulmonary edema and chronic respiratory failure.[53b]

Obstruction to lymphatic drainage (e.g., with carcinomatosis[1]) is an uncommon primary cause of pulmonary edema. However, in the presence of other predisposing factors, partial lymphatic obstruction or dysfunction would increase the tendency for edema formation. Studies in sheep have shown that normal contractions in lymphatic vessels and lymph flow are significantly inhibited by anesthesia and endotoxin infusion.[3] Systemic venous hypertension also impedes the flow of lymph into the central venous pool.

Re-expansion pulmonary edema may occur when a previously collapsed lung lobe is suddenly inflated. There may be correlations between the vigor of re-expansion, duration of collapse, and degree of edema. Damage to the capillary endothelium can occur, with both elevations in edema protein content and biochemical changes similar to those found with reperfusion injury.[12, 55–57a]

Pulmonary edema secondary to upper airway obstruction has also been reported in dogs[58] and is well recognized in humans.[59, 60] The pathogenesis is multifactorial, probably involving increased intrapleural and microvascular pressures as well as microvascular permeability changes.

On the basis of the Starling relationship, low plasma colloid osmotic pressure theoretically could induce pulmonary edema. Severe hypoproteinemia is rarely implicated as the sole cause of edema, although it does exacerbate edema generated by other mechanisms.[1, 2] In the dog with normal plasma proteins, edema will not occur until left atrial pressure rises above 23 mmHg. But when the plasma protein level is decreased by 50 percent, edema forms at a left atrial pressure of only 12 mmHg.[61]

Acute pulmonary hypertension could lead to pulmonary edema. Regional inhomogeneity of arteriolar vasoconstriction might protect some but not all pulmonary capillary beds from high microvascular pressures. The absence of clinically significant edema in chronic pulmonary hypertension probably relates to structural arteriolar changes that protect the capillary bed from excessive pressures.

Rarely, pulmonary edema of uncertain pathogenesis has been associated with other causes. It has been reported with hypoglycemia[50] and with ketamine HCl administration in cats.[26] It occurs in some people exposed to high altitudes but has not been reproduced in experimental animals.[12] Lastly, near drowning can flood alveoli and damage capillaries, causing pulmonary edema.[25, 62, 63]

PATHOPHYSIOLOGIC ALTERATIONS CAUSED BY PULMONARY EDEMA

STAGES OF PULMONARY EDEMA DEVELOPMENT

The sequence of edema accumulation appears to be similar, regardless of cause. Initially, there is a compensatory increase in lymphatic flow, which maintains normal interstitial volume (Stage 1). When the amount of capillary filtrate exceeds the pumping capacity of the lymphatics, fluid and colloid accumulate in the interstitial areas around bronchioles, arterioles, and venules (Stage 2).[3] Enlarged lymphatics and free fluid form a cuff around the bronchioles and pulmonary blood vessels.

During the early stages of edema, gas exchange may

be relatively unaffected if there is no increase in alveolar-capillary membrane thickness along the thin side of the interstitial space.[2, 3, 64] As capillary filtrate continues to accumulate, the less compliant interstitium around the alveolar-capillary septa also fills, interstitial pressure rises, and alveolar flooding begins.[1, 4, 15] Fluid initially accumulates in the corners of the alveoli where the radii of curvature are smallest (Stage 3A).[3, 9, 10] Finally, alveolar flooding occurs (Stage 3B).

There is controversy regarding mechanisms of fluid entry into the alveoli. Fluid may enter by retrograde flow from bronchioles[3, 12, 16], however, if the alveolar membranes have been disrupted, fluid can directly enter the alveolar space.[10, 22] Alveolar flooding, previously thought to be an all-or-none phenomenon with respect to an individual alveolus appears to occur gradually.[9] If there has been minimal alveolar-capillary membrane injury, clearing of the edema fluid can progress quickly once the initiating cause is relieved; the alveolar epithelium plays an active role.[3]

As more alveoli are flooded, total pulmonary gas exchange deteriorates. Flooded alveoli act as small regions of pure shunt, since no ventilation occurs; accordingly, the degree of arterial hypoxemia is related to the number of unventilated units.[1, 2, 15] During the late stages of edema, frothy fluid spills from the alveoli into the airways. Any nonflooded alveoli behind a froth-filled airway will be unventilated due to airway obstruction.[1, 2] Capillary membrane damage allows extravasation of red cells, which tint the froth pink.

The distribution of pulmonary edema across the lung is not homogeneous. Since mean intravascular pressures are greatest in the most ventral areas of the lung (Zone 3), where venous pressure exceeds alveolar pressure, venous congestion or disrupted alveolar-capillary membranes promote the most rapid and greatest accumulation of pulmonary edema here.[3] Although more edema accumulates in lower lobes, there also appears to be marked inhomogeneity of interstitial and alveolar edema distribution at any level within the lung; flooded alveoli can also border nonflooded units. Although gravity contributes to the greater amount of pulmonary fluid found in more ventral regions, other factors are involved as well.[9–11] Regional differences in apparent protein content of hydrostatic edema fluid, as well as the amount of edema, imply regional differences in the reflection coefficient for albumin.[9–11] Structural heterogeneity in the lymphatic system, and/or variation in the distribution of pulmonary blood flow or mediators of vascular tone, may also be important in determining the distribution of pulmonary edema of any cause.[9, 11, 65]

The venous congestion of cardiogenic edema causes an initial increase in pulmonary blood volume, with redistribution of flow and better perfusion dorsally.[15, 64] Greater formation and gravitation of pulmonary edema ventrally cause more marked airway and vascular compression in the dependent areas of the lung and also promote redistribution of blood flow. Pulmonary arteriolar vasoconstriction secondary to alveolar hypoxia is more prominent ventrally and may contribute to redistribution.[1, 3]

Reduced lung compliance (the ease with which the lung can be expanded) is an early feature of pulmonary edema. Compliance becomes severely impaired as edema progresses. As the lung becomes stiffer (noncompliant), there is an increased tendency for lung collapse.[1, 2] With advancing Stage 2 edema, fluid cuffs compress blood vessels and bronchi, isolating them from the normal inspiratory retracting forces of the surrounding lung.[64] Narrowing and premature expiratory closure of ventral (dependent) small airways are accentuated, especially in older animals and during recumbency. The resulting elevation in peripheral airway and vascular resistances promotes ventilation-perfusion mismatching at various levels within the lung.[15, 64] If alveoli flood, surface tension increases and flooded units shrink in size, further decreasing lung compliance. Small airway closure throughout the respiratory cycle and alveolar flooding cause a true intrapulmonary shunt.

At higher lung volumes, pulmonary compliance abnormalities and small airway closure are minimized.[64] Thus, if several deep breaths can be stimulated during therapy, ventilation should improve. Airway narrowing may also be exacerbated by reflex bronchoconstriction.[1, 66] Chronic interstitial edema and high pulmonary capillary pressures induce reactive tissue changes and lung fibrosis, which decrease pulmonary compliance as well.[15]

A shallow, rapid breathing pattern occurs with pulmonary edema, which minimizes the work of ventilating the stiff lungs. Increased stimulation of airway and interstitial pulmonary receptors occurs secondary to pulmonary venous congestion and edema. This results in a vagally mediated reflex increase in respiratory rate.[3, 67–70] Tachypnea may ameliorate the accumulation of edema by increased pumping of the lymph vessels.

Arterial oxygenation (PaO_2) decreases because of ventilation-perfusion mismatch. Animals with reduced cardiac output also have a decreased mixed venous PO_2, which leads to decreased PaO_2 for any level of ventilation-perfusion mismatch. Hypoxic pulmonary vasoconstriction is an attempt to minimize this mismatch by redirecting blood flow away from unventilated alveoli and by redistributing flow toward the better ventilated apices of the lung.[64] The $PaCO_2$ tends to be normal or low. Hyperventilation of unaffected alveoli occurs with tachypnea; since CO_2 diffuses more rapidly than O_2 and dogs have good collateral ventilation, hypercapnia occurs only with fulminant edema.[1] Both hypo- and hypercapnia can worsen ventilation-perfusion mismatch. However, experimentally, artificial hyperventilation to reduce $PaCO_2$ was associated

with reduced PaO_2 and increased alveolar-arterial O_2 gradient.[71]

CLINICAL MANIFESTATIONS

HISTORY AND PHYSICAL EXAMINATION

The historical and physical findings associated with pulmonary edema vary with the severity of fluid accumulation. Mild edema can cause tachypnea or exertional dyspnea. In dogs there may be a dry frequent cough of recent onset, although bronchial compression from left atrial enlargement may cause a similar cough. Cats are much less likely to cough with pulmonary edema. Orthopnea may develop as edema worsens; affected dogs tend to stand with elbows abducted and are reluctant to lie down (see Fig. 5–1), whereas cats tend to hunch in a sternal position with elbows abducted. Respirations become more rapid and shallow. Paroxysms of dyspnea and coughing often occur after resting or during recumbency as added blood volume is returned from the extremities to the central pool.[12] Hyperpnea or dyspnea worsens with hypoxemia, especially at PaO_2 less than 60 mmHg, and with lactic acidosis.[15] With severe edema, Cheyne-Stokes respiration, expectoration of pink foam, and cyanosis may occur. Open-mouth breathing in the cat often signals severe respiratory distress.

AUSCULTATION

Auscultatory findings also vary. There may be no abnormalities with early interstitial edema. In peracute edema, only loud bronchial sounds may be heard. As small airways become compressed, fine crackles may be heard on inspiration as previously closed bronchioles snap open. Initially, crackles may be heard only ventrally at end-inspiration after a deep breath. It is helpful to hold off the animal's breath for a short time to stimulate deep inspiration. As edema worsens, wheezes and crackles of varying pitch and more widespread distribution are often heard during both inspiration and early expiration.

It is important to remember that abnormal respiratory sounds are not specific for pulmonary edema. Similarly, even severe lung edema may not lead to obvious adventitial sounds. Other lung diseases, especially pulmonary fibrosis and bronchitis, are associated with loud crackles and wheezes. Thus, abnormal lung sounds must be evaluated within the context of history, physical findings, cardiac auscultation, thoracic radiography, and ancillary tests.

DIAGNOSIS

Early detection of pulmonary edema is often difficult. Despite advances in diagnosis with CT scans and

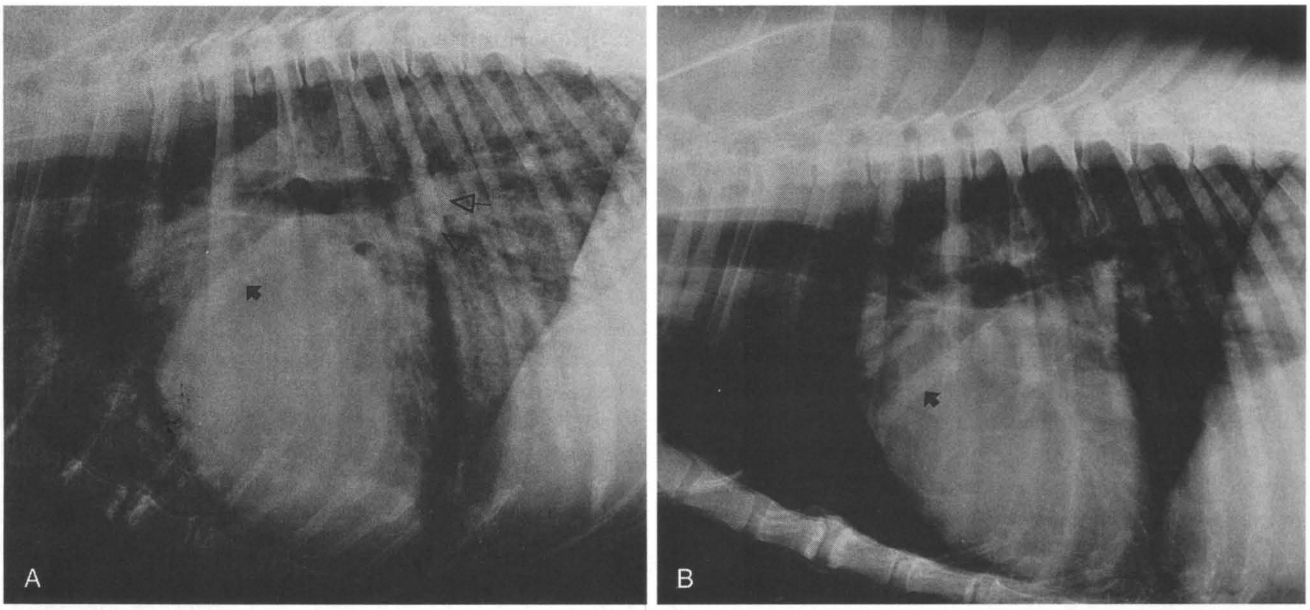


FIGURE 13–2

Lateral radiographs from an 11-year-old Afghan hound with dilated cardiomyopathy and mitral insufficiency taken during congestive heart failure (CHF) (A) and after therapy (B). (A) Radiographic changes compatible with left-sided CHF include a marked, diffusely increased pulmonary opacity throughout the lung fields, air bronchograms, and a large lobar pulmonary vein *(closed arrow)*. The left atrium is moderately enlarged *(open arrows)*. (B) Post therapy radiograph. Notice that the lung fields are considerably reduced in opacity compared with the pretreatment radiograph. The pulmonary vein is still distended *(arrow)*, indicating pulmonary venous congestion. The left atrium is prominent, and the cardiac silhouette is mildly enlarged.

double-indicator dilution techniques,[15] radiography remains the most practical diagnostic modality.[72] A persistent increase in resting respiratory rate may signal early pulmonary edema. Measurement of pulmonary artery occlusion ("capillary wedge") pressure may be used to estimate pulmonary capillary and left atrial pressures, but this may not reflect actual pulmonary capillary pressure when pulmonary vascular resistance is elevated.[8] In a human study, wedge pressure underestimated capillary pressure by a mean of 7 mmHg.[3] Presently, invasive hemodynamic monitoring is still not readily accessible for most veterinary practitioners.

RADIOGRAPHY

The characteristic locations of lung infiltrates and the caliber of pulmonary vessels can suggest a radiologic diagnosis of pulmonary edema and may help the clinician distinguish between cardiogenic and noncardiogenic edema. The technical quality of the radiograph, patient positioning, phase of respiration, and any artifacts should be considered before a presumptive diagnosis of lung edema is made. Pre-existing chest pathology and the time lag between edema formation and the appearance of radiographic abnormalities may complicate the radiographic diagnosis.[15, 15a]

The onset of left-sided congestive heart failure is associated with pulmonary venous congestion. In the dog, the usual radiographic signs are dilated pulmonary veins and increased symmetric perihilar interstitial opacities. On the lateral view, the location of cranial pulmonary vessels (from dorsal to ventral) are lobar artery, bronchus, lobar vein. Normally, the width of the vein and artery are equal and average 70 to 75 percent of the diameter of the dorsal one third of the fourth rib. On the dorsoventral or ventrodorsal view, the lobar artery is craniolateral to the vein and associated bronchus. As pulmonary congestion increases, the width and opacity of the pulmonary veins exceed that of the accompanying arteries (Fig. 13–2; see also Fig. 7–20). Sometimes the cranial lobar vein appears to sag down, away from the bronchus on lateral view.

Although pulmonary venous distention is a significant indicator of left-sided congestive heart failure, it is not a consistent finding. Secondary right-sided heart failure or compensatory venoconstriction will reduce the engorgement of pulmonary veins.

Cats with severe pulmonary edema frequently exhibit enlargement of both lobar vein and artery. As with dogs, this is not a consistent finding.

Cardiomegaly is common when left-sided heart failure is caused by chronic mitral regurgitation, dilated cardiomyopathy, or congenital left-to-right shunts. Typical radiographic changes in the cardiac silhouette are described elsewhere (chapter 7).[72–74] However, radiographic signs of heart enlargement may be minimal in some cases of hypertrophic cardiomyopathy, acute endocarditis or ruptured chordae tendineae with mitral insufficiency, acute myocardial failure, tachyarrhythmias, or constrictive pericarditis.

Pulmonary parenchymal opacities appear as edema develops. Interstitial fluid blurs the edges of pulmonary vessels and cuffs the bronchi, especially in the hilar region of dogs. Pleural thickening may be seen, but because dogs and cats have little interlobular tissue, Kerley's lines—a feature of pulmonary edema in humans—do not appear. Chronic edema stimulates interstitial lung fibrosis and adds to the overall increase in radiographic opacity.[72]

Early alveolar edema, in which groups of flooded alveoli intermingle with aerated units, is radiographically evident as areas of fluffy or mottled soft tissue opacity. As alveolar flooding progresses, these areas become more confluent. Eventually, a homogeneous opacity develops with completely obscured pulmonary vessels and the appearance of air bronchograms (see Fig. 13–2; Fig. 13–3). Interlobar borders may be visualized, indicating subpleural edema or pleural fluid.[72]

The limitations of thoracic radiography in detecting and quantifying pulmonary edema must be recognized (chapter 7). For example, a time lag exists between the onset and clearance of pulmonary fluid and its radiographic appearance and disappearance. Thus, the animal may clinically seem better or worse than radiographs indicate. Small changes in interstitial opacity are difficult to appreciate, and pre-existing lung pathology may hinder the identification of pul-

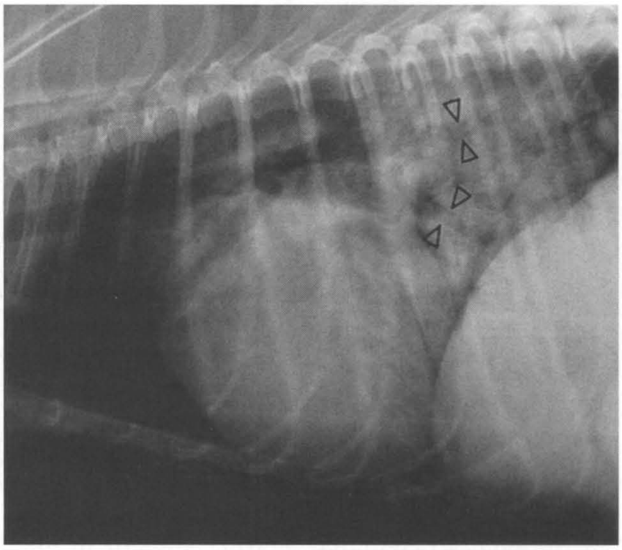


FIGURE 13–3

Lateral radiograph from an 11-year-old poodle with congestive heart failure due to mitral regurgitation. Moderate generalized cardiomegaly is present. The left atrium is prominent. Interstitial and alveolar infiltrates compatible with pulmonary edema are evident dorsally, caudally, and in the perihilar region. They result in air bronchograms *(arrowheads)*. Pulmonary interlobar borders are visualized. Diuretic therapy led to prompt radiographic clearing of these pulmonary opacities.

monary edema.[72] After diuretic therapy, the radiographic evidence of pulmonary edema may be minimal even though some patients still exhibit clinical signs.

Cardiogenic edema in dogs accumulates to a greater extent in the hilar region (see Fig. 13–3). This edema is usually bilaterally symmetric, although it is not uncommon to observe greater involvement of the right lobes.[72] Hypostatic fluid accumulation in a recumbent animal can also cause an asymmetric radiographic appearance, though lateral recumbency is uncommon in dyspneic animals. The distribution of pulmonary edema in dogs with fulminant congestive heart failure may be diffuse (see Fig. 13–2*A*).

Cardiogenic pulmonary edema in cats can be diffuse, but in contrast to dogs, it often appears unevenly distributed, patchy, or concentrated in the middle lung zones (Fig. 13–4). Differentiation from other infiltrative lung lesions, therefore, can be more difficult in the cat.

When lung infiltrates are present in a lobar, asymmetric, or otherwise uncharacteristic pattern for cardiogenic edema, other etiologies should also be considered (e.g., pneumonia, thromboembolism, neoplasia, obstructive lung disease), as well as noncardiogenic edema.[74a] Neurogenic edema (Fig. 13–5) tends to be distributed dorsocaudally in the lung periphery.[50, 75]

TREATMENT OF PULMONARY EDEMA

Therapeutic objectives for pulmonary edema of any cause include (1) restoration of arterial oxygenation, (2) removal of alveolar fluid, and (3) correction of the underlying etiology (Table 13–1). Mainstays of therapy include supplemental oxygen, airway suction (if frothing is evident), redistribution of pulmonary blood to the peripheral circulation, rest, and diuresis. The patient should be handled gently to minimize stress. Whenever possible, oral medications should be avoided in dyspneic animals.

SUPPLEMENTAL OXYGEN

Oxygen can be administered by face mask, nasal catheter, endotracheal tube, or O_2 cage. An O_2 cage

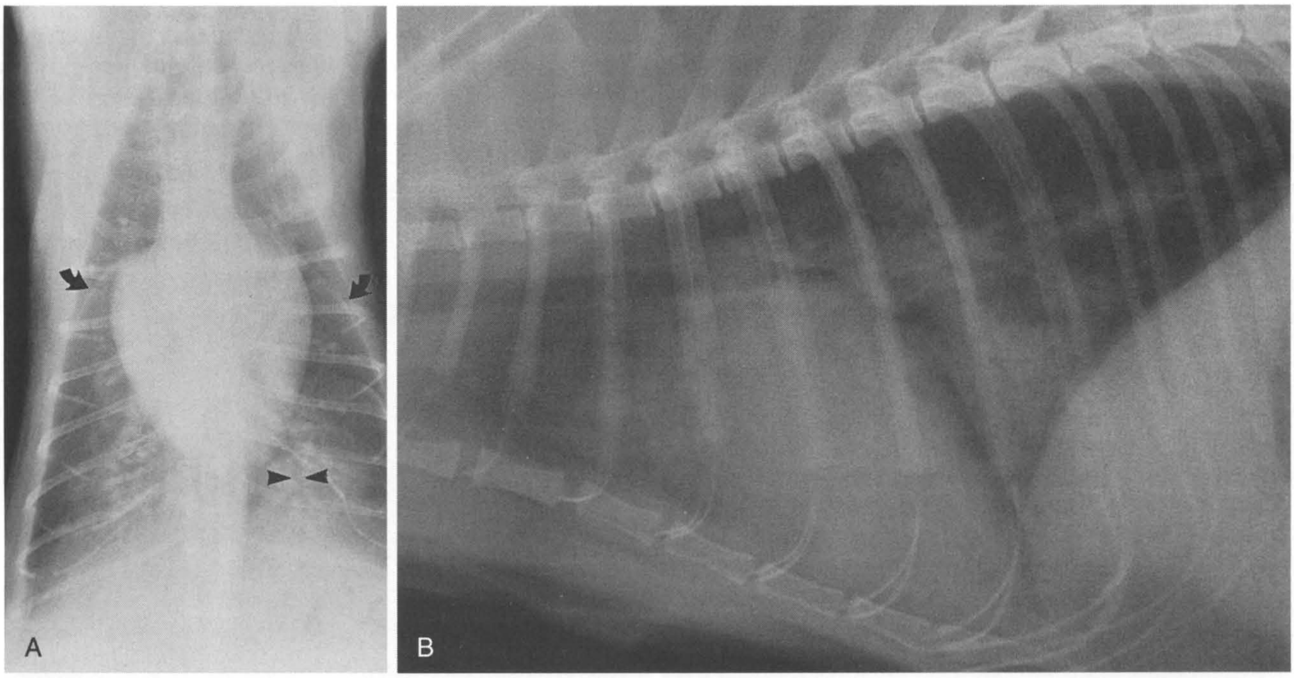


FIGURE 13–4

Radiographs from two cats with cardiomyopathy and left-sided congestive heart failure. (A) Ventrodorsal view of one cat with cardiogenic pulmonary edema. The heart is moderately enlarged. Left ventricular enlargement is evident by cardiac elongation; the left auricle is rounded and enlarged and the right atrium is also prominent. Pulmonary edema is suggested by bilateral interstitial and alveolar infiltrates, which are most prominent caudal to the heart. An air bronchogram sign is evident in the left caudal lobe *(arrowheads)*. A small pleural effusion is present, resulting in prominent interlobar fissures *(curved arrows)* and blunted costophrenic angles. (B) Lateral view of a different cat with hypertrophic cardiomyopathy illustrating interstitial and alveolar lung opacities. There is a predisposition to the caudal lung lobes, although some patchy infiltrates are also observed cranial to the heart. Moderate cardiomegaly is present in both views.

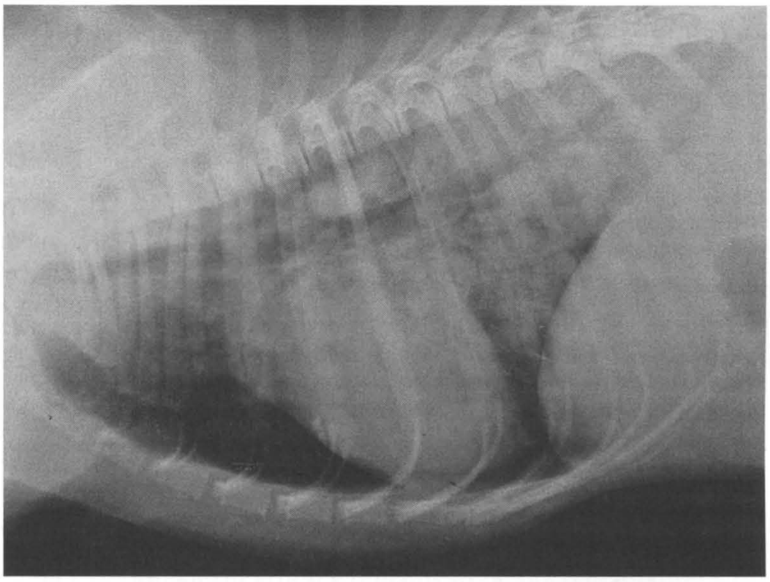


FIGURE 13–5

Lateral radiograph from an 18-month-old Siberian husky with noncardiogenic pulmonary edema secondary to seizure. The cardiac silhouette is normal sized (compare with Figs. 13–2 and 13–3). A profound increase in pulmonary interstitial and alveolar opacities with air bronchograms is evident in the caudal lung lobes. The dorsocaudal lung fields display particularly increased opacity, typical of neurogenic pulmonary edema.

should have temperature and humidity controls; a maximum of 65° F has been recommended for normothermic animals.[25] Oxygen flows of 6 to 10 L/min are usually adequate. Initially, administered concentrations of 50 to 100 percent O_2 may be necessary.

Severely affected animals, or those that experience respiratory arrest, may respond to endotracheal or tracheotomy tube placement and mechanical ventilation with positive end-expiratory pressure (PEEP), continuous positive airway pressure (CPAP), or high-frequency jet ventilation. Salutary effects of PEEP ventilation include clearing of small airways, expanding small-volume alveoli, forcing alveolar fluid back into the interstitium, and increasing lung volume to augment the interstitial fluid capacity.[12, 76a]

Chronically administered high O_2 concentrations (> 70%) can injure lung tissue. A formula has been devised for humans using an initial FiO_2 (inspired O_2 concentration) of less than 50 percent. Therapy is adjusted by adding increments of 5 mmHg PEEP until the PaO_2 divided by the FiO_2 is greater than 300.[64] Alternatively, PEEP can be achieved with spontaneous ventilation through a respirator and by exhaling against a 4- to 20-cm H_2O pressure.[25, 77] More information on ventilatory support is found elsewhere.[78–80]

Careful, continuous monitoring is essential for intubated animals. Mechanical ventilation with high peak inspiratory pressures has been shown to produce high-permeability pulmonary edema.[81, 82]

DRUG THERAPIES

DIURETICS

Rapid diuresis and pulmonary fluid reabsorption is a primary concern of initial therapy and can be achieved with intravenous administration of furosemide.[83] This loop-acting diuretic may also reduce pulmonary shunt by augmenting perfusion of nonflooded alveoli before diuresis occurs.[84] Furosemide must be delivered to the nephron by renal blood flow, which may be impaired in severe heart failure. Some patients are unresponsive to traditional doses (1 to 2 mg/kg) of furosemide but will respond to higher initial doses or to cumulative doses administered every 30 to 60 minutes. Accordingly, we usually administer relatively high IV or IM doses initially (2 to 5 mg/kg) to assure delivery of a sufficient concentration of the drug to the renal tubules. Furosemide must be actively secreted in the proximal tubules, delivered to the loop of Henle, and sufficiently concentrated there to induce diuresis. Once diuresis has ensued and respiratory signs begin to abate, the dosage should be reduced (0.5 to 2 mg/kg every 8 to 12 hours) to prevent excessive volume contraction or electrolyte depletion.[84a] Low sodium water should be offered to the patient. In very ill, azotemic, or anorectic animals, conservative fluid therapy may be required. Indirect monitoring of arterial blood pressure, serial determination of serum creatinine and BUN, and regular measurement of serum electrolytes are practical and effective methods for avoiding overdiuresis in most patients. Other diuretics, such as bumetanide, the thiazides, or aldosterone antagonists (spironolactone), can be helpful either alone or in conjunction with oral furosemide in treating chronic pulmonary edema in dogs. Pulmonary edema in cats is usually responsive to furosemide (1 to 2 mg/kg) or furosemide and transdermal nitroglycerin.

BRONCHODILATORS

Methylxanthines such as aminophylline, given intramuscularly or by slow intravenous injection, have mild

TABLE 13–1
Hospital Therapy of Pulmonary Edema

Avoid All Stress!

Avoid Significant IV Fluid Administration

Restore Oxygenation

Check airway patency
Give supplemental O_2 (avoid > 50% for > 48 hr)
Provide cage rest
Intubate/supply positive-pressure ventilation if needed
If frothing is evident, suction the airways

Rapidly Remove Alveolar Fluid

Redistribute blood volume:
  Morphine (dogs only; see below)
  Vasodilators:
    2% nitroglycerin ointment (dogs: $\frac{1}{2}-1\frac{1}{2}$ inch topically q 12 hr; cats: $\frac{1}{8}-\frac{1}{4}$ inch q 8–12 hr)
    Na^+ nitroprusside (0.5–5 μg/kg/min CRI)
Initiate diuresis:
  Furosemide (dogs: 2–5 mg/kg IV, IM q 6–8 hr; cats: 2–4 mg/kg IV, IM q 6–8 hr)
  Following initial diuresis, decrease dose and repeat q 8–12 hr

Reduce Anxiety

Morphine (dogs: 0.05–0.1 mg/kg IV; 0.1–0.5 mg/kg SC or IM)
Acepromazine (cats: 0.1 mg/kg IM, SC q 8–12 hr) mixed with butorphanol (0.15 mg/kg IM, SC q 8–12 hr)

Reduce Bronchoconstriction

Aminophylline (dogs: 6–10 mg/kg IV, PO, can repeat q 6 hr; cats: 4–8 mg/kg PO, can repeat q 12 hr)

Administer Inotropic Support (for myocardial failure)

Digoxin (dogs: 0.01–0.015 mg/kg PO ÷ bid; cats: 0.031 mg total dose PO q 48 hr)
Dobutamine (2–10 μg/kg/min CRI)
Dopamine (2–8 μg/kg/min CRI)

Increase Cardiac Output and Reduce Afterload (see text)

Na^+ nitroprusside (see earlier dosage)
Hydralazine (dogs: 1–3 mg/kg PO, q 12 hr)

Treat High-Permeability Edema

Consider glucocorticoids
Institute specific measures depending on etiology

Provide Ancillary Therapy

Correct acid-base imbalance (e.g., sodium bicarbonate if moderate to severe metabolic acidosis; ventilation for respiratory acidosis)
Provide thoracocentesis if concurrent pleural effusion and atelectasis

Monitor the Patient

Record heart rate and rhythm (ECG), pulse strength, arterial blood pressure, respiratory rate, hydration status, urinary output
Monitor pulse oximetry, arterial blood gases, end-tidal CO_2 (if intubated)
Measure PCV/plasma protein, serum biochemistries, and electrolytes

CRI, constant rate infusion; ECG, electrocardiogram; PCV, packed cell volume.

diuretic and positive inotropic actions as well as a bronchodilating effect. They also decrease fatigue of respiratory muscles and enhance diaphragmatic function.[84b] Rapid absorption occurs after oral administration. Adverse effects include increased sympathomimetic activity and arrhythmias, especially with parenteral administration. Objective measures of efficacy in pulmonary edema are lacking.

TRANQUILIZERS

Dogs with severe pulmonary edema may benefit from morphine sulfate administered every 2 to 3 minutes (0.05 to 0.1 mg/kg) intravenously until the desired clinical response is achieved,[76] or administered as a single intramuscular or subcutaneous dose (0.1 to a maximum of 0.5 mg/kg).[26] Beneficial effects include reduced anxiety, slower, deeper breathing from respiratory center depression, and redistribution of blood away from the lungs via splanchnic vasodilation. Morphine can raise intracranial pressure and is contraindicated in neurogenic edema. Morphine is also contraindicated in cats. Acepromazine (0.1 mg/kg SQ) mixed with butorphanol (0.15 mg/kg SQ) can be used as an alternative for cats. Although peripheral redistribution of blood might be promoted, these drugs may exacerbate pre-existing hypothermia.

VASODILATORS

Vasodilator drugs, such as 2 percent nitroglycerin ointment applied cutaneously or intravenous nitroprusside, a rapid-acting arteriovenous dilator (used with careful patient and blood pressure monitoring), can reduce fulminant edema by increasing systemic venous capacitance and lowering pulmonary venous pressure. Nitroprusside may also improve cardiac output by systemic arteriolar dilation.

Treatment of acute, severe edema resulting from mitral regurgitation may be improved when oral hydralazine, a pure arteriolar dilator, is added to diuretic and topical nitroglycerin administration. Hydralazine or nitroprusside should be chosen over angiotensin-converting enzyme (ACE) inhibitors for acute therapy. The onset of action for hydralazine begins within approximately 30 minutes and peaks within 3 hours.[85] In contrast, ACE inhibitors have a longer onset of action and later peak activity (chapters 12, 25).

CARDIOTONICS

Positive inotropic drugs, when indicated, must be used carefully. Catecholamines can increase pulmonary and systemic vascular resistance, potentially exacerbating interstitial fluid accumulation. The acidosis and hypoxemia that are common in severe edema can increase myocardial sensitivity to digitalis-induced arrhythmias.[64] Monitoring electrolytes and acid-base balance is important.

ADDITIONAL MEASURES

Other techniques used for acute cardiogenic edema include phlebotomy of up to 25 percent of total blood volume and rotating tourniquets (not very effective in

animals). A newer technique reported in humans is venous ultrafiltration with fluid subtraction.[85a]

SPECIFIC TREATMENT PLANS

CANINE MITRAL REGURGITATION

Initial therapy of pulmonary edema is directed to induce diuresis with furosemide, lower venous pressures further with topical nitroglycerin ointment, and provide supplemental oxygen. Dogs with mild-to-moderate signs usually respond well to such treatment.

More aggressive therapy is needed for life-threatening pulmonary edema. In addition to high-dose furosemide, nitroglycerin, and oxygen, hydralazine is administered at an initial dose of 0.75 to 1 mg/kg PO, followed by repeated doses every 2 to 3 hours, if needed, to lower the systolic blood pressure to between 90 and 110 mmHg, or until obvious clinical improvement. Hydralazine effectively reduces regurgitant fraction and lowers left atrial pressure (chapter 12).[85a] If blood pressure cannot be monitored, an initial dose of 1 mg/kg is given and repeated in 2 to 4 hours if sufficient clinical improvement has not been observed. If necessary, administration of 1 to 2 mg/kg can be repeated every 12 hours.

An alternative therapy to nitroglycerin/hydralazine is sodium nitroprusside infusion beginning at 1 μg/kg/min. The dose should be titrated to yield a systolic blood pressure of 90 to 100 mmHg. The infusion is usually continued for 12 to 24 hours (Fig. 13–6). Following successful therapy of pulmonary edema, chronic treatment can be initiated with maintenance doses of furosemide, an ACE inhibitor, and in most cases, digoxin (chapter 12).

FELINE HYPERTROPHIC CARDIOMYOPATHY

Initial therapy for pulmonary edema includes furosemide, nitroglycerin ointment, and oxygen. Most cats respond well to this treatment. Once diuresis has occurred, echocardiography and other clinical studies can be completed as indicated. Chronic therapy usually includes diltiazem or a β-adrenergic blocker. The dose of furosemide is tapered to the lowest effective maintenance dose or, in some cases, discontinued[84a] (chapter 28). Many clinicians also prescribe an ACE inhibitor (enalapril, 0.25 to 0.5 mg/kg daily), although long-term efficacy remains to be documented.

DILATED CARDIOMYOPATHY

Initial therapy of pulmonary edema related to cardiogenic shock in canine dilated cardiomyopathy usually includes furosemide, oxygen, and dobutamine or dopamine infusion (chapter 27). The administration of potent inotropic agents (dopamine, dobutamine) can increase cardiac output and blood pressure, allowing safe administration of vasodilator drugs. For life-threatening pulmonary edema, sodium nitroprusside (beginning at 0.5 μg/kg/min in a constant rate infusion) is very effective with blood pressure monitoring. Alternatively, topical nitroglycerin ointment and an ACE inhibitor can be used in less severe cases. Digitalization is indicated and is particularly important

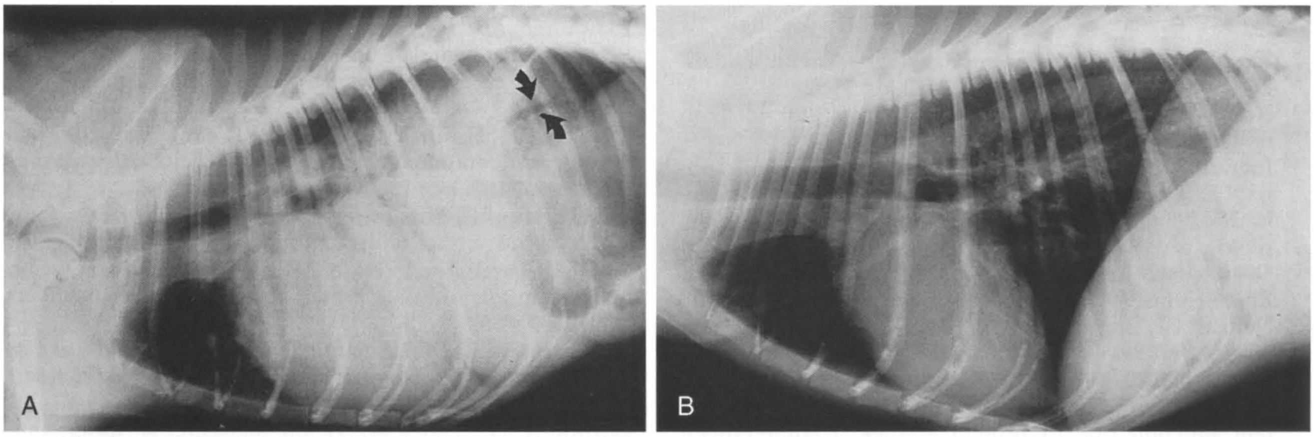


FIGURE 13–6

(A) Lateral radiograph from a dog with severe alveolar cardiogenic pulmonary edema resulting from rupture of chordae tendineae. There is only mild-to-moderate cardiomegaly, with a marked increase in pulmonary opacity. A number of air bronchogram signs are evident *(arrows)*. (B) Repeat lateral radiograph exposed 72 hours after the radiograph depicted in (A). Following aggressive diuresis with furosemide and vasodilator therapy with sodium nitroprusside, the pulmonary edema has resolved. The heart has decreased in size due to volume contraction and preload reduction.

if there is concurrent atrial fibrillation. After 24 to 48 hours of intensive therapy, chronic treatment can usually be initiated, which includes digoxin, furosemide, an ACE inhibitor, and dietary sodium restriction. Oral hydralazine can be added in refractory cases.

THERAPY OF NONCARDIOGENIC EDEMA

Pulmonary edema associated with severe alveolar-capillary membrane damage and inflammation is difficult to treat successfully.[74a, 76a] Experimentally, a variety of substances that may protect against or counteract the effects of different inflammatory mediators have been administered either before or after induction of high-permeability edema.[39, 86–88] Oxygen therapy is given as outlined earlier. A diuretic may be helpful, but blood pressure and hydration should be monitored. The tendency to infuse large volumes of crystalloid must be tempered with an understanding that increasing pulmonary blood flow usually worsens noncardiogenic edema. Although use of corticosteroids is controversial, they have been advocated in the early treatment of smoke inhalation, electric shock, snake bite, septic shock, and anaphylaxis.[64] Identification of the primary etiology, if possible, may suggest additional therapy. If PaO_2 falls to < 60 mmHg despite supplemental oxygen, if PCO_2 is > 50 mmHg, or if respiratory fatigue is evident, the patient should be ventilated. Additional therapy for high-permeability edema has been reviewed elsewhere.[25, 76a, 89–91]

REFERENCES

1. West JB. Pulmonary pathophysiology—The essentials. 2nd ed. Baltimore, Williams & Wilkins, 1982
2. Nonn JF. Applied Respiratory Physiology. 2nd ed. London, Butterworths, 1977
3. Ingram RH, Braunwald E. Pulmonary edema. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB Saunders, 1992, p 551
4. Guyton AC. Textbook of Medical Physiology. 7th ed. Philadelphia, WB Saunders, 1986, p 466
5. Neiman GF, Brendenberg CE. High surface tension pulmonary edema induced by detergent aerosol. J Appl Physiol 58:129, 1985
6. Seeger W, Stohr G, Wolf HRD, et al. Alteration of surfactant function due to protein leakage. J Appl Physiol 58:326, 1985
7. Cottrell TS, Levine OR, Senior RM, et al. Electron microscopic alterations at the alveolar level in pulmonary edema. Circ Res 21:783, 1967
8. Cope DK, Grimbert F, Downey JM, et al. Pulmonary capillary pressure: A review. Crit Care Med 20:1043, 1992
9. Bachofen H, Schürch S, Michel RP, et al. Experimental hydrostatic pulmonary edema in rabbit lungs—Morphology. Am Rev Respir Dis 147:989, 1993
10. Bachofen H, Schürch S, Michel RP, et al. Experimental hydrostatic pulmonary edema in rabbit lungs—Barrier lesions. Am Rev Respir Dis 147:997, 1993
11. Crapo JD. New concepts in the formation of pulmonary edema. Am Rev Respir Dis 147:790, 1993
12. Uhley HN, Leeds SE, Sampson JJ, et al. Role of pulmonary lymphatics in chronic pulmonary edema. Circ Res 11:966, 1962
13. Enderson BL, Rice CL, Beaver CW, et al. High frequency ventilation and the accumulation of extravascular lung water. J Surg Res 36:433, 1984
14. Weaver LJ, Carrico CJ. Congestive heart failure and edema. *In* Staub NC, Taylor AE (eds): Edema. New York, Raven Press, 1984, p 543
15. Staub NC. Pathophysiology of pulmonary edema. *In* Staub NC, Taylor AE (eds): Edema. New York, Raven Press, 1984, p 719

15a. Takeda A, Okumura S, Miyamoto T, et al. Comparison of extravascular lung water volume with radiographic findings in dogs with experimentally increased permeability pulmonary edema. J Vet Med Sci 57:481, 1995

16. Staub NC. New concepts about the pathophysiology of pulmonary edema. J Thorac Imaging 3:8, 1988
17. Lang SA, Maron MB. Hemodynamic basis for cocaine-induced pulmonary edema in dogs. J Appl Physiol 71:1166, 1991
18. Hering SE, Jurca M, Vichi FL, et al. Reversible cardiomyopathy in patients with severe scorpion envenoming by *Tityus serrulatus*: Evolution of enzymatic, electrocardiographic and echocardiographic alterations. Ann Trop Paediatr 13:173, 1993
19. Miller WC, Simi WW, Rice DL. Contribution of systemic venous hypertension to the development of pulmonary edema in dogs. Circ Res 43:598, 1978
20. Butler BD, Drake RE, Sneider WD, et al. Changes in microvascular permeability with acceleration of edema in dog lungs. Am J Physiol 258:H395, 1990
21. West JB, Mathieu-Costello O. Stress failure of pulmonary capillaries in the intensive care setting. Schweiz Med Wochenschr 122:751, 1992
22. Tsukimoto K, Mathieu-Costello O, Prediletto R, et al. Ultrastructural appearances of pulmonary capillaries at high transmural pressures. J Appl Physiol 71:573, 1991
23. Cohen AB, Stevens MD, Miller EJ, et al. Neutrophil-activating peptide-2 in patients with pulmonary edema from congestive heart failure or ARDS. Am J Physiol 264:L490, 1993
24. Kuida H, Hinshaw LB, Gilbert RP, et al. Effect of gram-negative endotoxin on pulmonary circulation. Am J Physiol 192:335, 1958
25. Hawkins EC, Ettinger SJ, Suter PF. Diseases of the lower respiratory tract and pulmonary edema. *In* Ettinger SJ (ed): Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat. 3rd ed. Philadelphia, WB Saunders, 1983, p 853
26. Bonagura JD. Pulmonary edema. *In* Kirk RW (ed): Current Veterinary Therapy VII. Philadelphia, WB Saunders, 1980, p 243
27. Toung TJ, Sendak MJ, Rosenfeld BA, et al. Lung injury produced by pancreatic proteases in dogs. Surgery 112:68, 1992
28. Isago T, Noshima S, Traber LD, et al. Analysis of pulmonary microvascular permeability after smoke inhalation. J Appl Physiol 71:1403, 1991
29. Ghio AJ, Kennedy TP, Hatch GE, et al. Reduction of neutrophil influx diminishes lung injury and mortality

following phosgene inhalation. J Appl Physiol 71:657, 1991
30. McDonald JW, Heffner JE. Eugenol causes oxidant-mediated edema in isolated perfused rabbit lungs. Am Rev Respir Dis 143:806, 1991
31. Lainee P, Robineau P, Guittin P, et al. Mechanisms of pulmonary edema induced by an organophosphorus compound in anesthetized dogs. Fundam Appl Toxicol 17:177, 1991
32. Royston BD, Webster NR, Nunn JF. Time course of changes in lung permeability and edema in the rat exposed to 100% oxygen. J Appl Physiol 69:1532, 1990
33. Yoshimura K, Nakagawa S, Koyama S, et al. Leukotriene B_4 induces lung injury in the rabbit: Role of neutrophils and effect of indomethacin. J Appl Physiol 74:2174, 1993
34. Patterson CE, Barnard JW, Lafuze JE, et al. The role of activation of neutrophils and microvascular pressure in acute pulmonary edema. Am Rev Respir Dis 140:1052, 1989
35. Herdon DN, Traber DL, Niehaus GD, et al. The pathophysiology of smoke inhalation injury in a sheep model. J Trauma 24:1044, 1984
36. Malik AB, Perlman MB, Cooper JA, et al. Pulmonary microvascular effects of arachidonic acid metabolites and their role in lung vascular injury. Fed Proc 44:36, 1985
37. Brigham KL. Metabolites of arachidonic acid in experimental lung vascular injury. Fed Proc 44:43, 1985
38. Horgan MJ, Palace GP, Everitt JE, et al. TNF-alpha release in endotoxemia contributes to neutrophil-dependent pulmonary edema. Am J Physiol 264:H1161, 1993
39. Jacobson JM, Michael JR, Meyers RA, et al. Hyperbaric oxygen toxicity: Role of thromboxane. J Appl Physiol 72:416, 1992
40. Welbourn R, Goldman G, Kobzik L, et al. Interleukin-2 induces early multisystem organ edema mediated by neutrophils. Ann Surg 214:181, 1991
41. Lantz RC, Keller GE, Burrell R. The role of platelet-activating factor in the pulmonary response to inhaled bacterial endotoxin. Am Rev Respir Dis 144:167, 1991
42. Seeger W, Grimminger F, Barden M, et al. Omega-oxidized leukotriene B_4 detected in the broncho-alveolar lavage fluid of patients with non-cardiogenic pulmonary edema, but not in those with cardiogenic edema. Intensive Care Med 17:1, 1991
43. Hocking DC, Phillips PG, Ferro TJ, et al. Mechanisms of pulmonary edema induced by tumor necrosis factor-alpha. Circ Res 67:68, 1990
44. Goldblum SE, Yoneda K, Cohen DDA, et al. Provocation of pulmonary vascular endothelial injury in rabbits by human recombinant interleukin-1 beta. Infect Immun 56:2255, 1988
44a. Heffner JE, Sahn SA, Repine JE. The role of platelets in the adult respiratory distress syndrome. Am Rev Respir Dis 135:482, 1987
44b. Frevert CW, Warner AE. Respiratory distress resulting from acute lung injury in the veterinary patient. J Vet Int Med 6:154, 1992
45. Barnard JW, Patterson CE, Hull MT, et al. Role of microvascular pressure in reactive oxygen-induced lung edema. J Appl Physiol 66:1486, 1989
46. Paterson IS, Klausner JM, Pugatch R, et al. Noncardiogenic pulmonary edema after abdominal aortic aneurysm surgery. Ann Surg 209:231, 1989
47. Wang CZ, Barrow RE, Cox CS, et al. Influence of detergent aerosol on lung microvascular permeability. J Appl Physiol 74:1016, 1993
48. Lord PF. Neurogenic pulmonary edema in the dog. J Am Anim Hosp Assoc 11:778, 1975
49. Vreim CE, Snashall PD, Staub NC. Protein composition of lung fluids in anesthetized dogs with acute cardiogenic edema. Am J Physiol 231:1466, 1976
50. Newman MM, Kligerman M, Willcox M. Pulmonary hypertension, pulmonary edema, and decreased pulmonary compliance produced by increased intracranial pressure in cats. J Neurosurg 60:1207, 1984
51. Bradley RL, Keating ML. Neurogenic pulmonary edema in a cat. Fel Pract 9:26, 1979
52. Kolata RJ. The clinical features of electrical cord bite injury in dogs. *In* Proceedings of the 41st Annual Meeting of the American Animal Hospital Association, 1974, p 460
53. Simon RP. Neurogenic pulmonary edema. Neurol Clin 11:309, 1993
53a. Drobatz KJ, Saunders M, Pugh CR, Hendricks JC. Noncardiogenic pulmonary edema in dogs and cats: 26 cases (1987–1993). J Am Vet Med Assoc 206:1732, 1995
53b. Jarvinen A-K, Saario E, Andresen E, et al. Lung injury leading to respiratory distress syndrome in young Dalmatian dogs. J Vet Intern Med 9:162, 1995
54. Maron MB. Pulmonary vasoconstriction in a canine model of neurogenic pulmonary edema. J Appl Physiol 68:912, 1990
55. Wilkinson PD, Keegan J, Davies SW, et al. Changes in pulmonary microvascular permeability accompanying re-expansion oedema: Evidence from dual isotope scintigraphy. Thorax 45:456, 1990
56. Jackson RM, Veal CF. Re-expansion, re-oxygenation and rethinking. Am J Med Sci 298:44, 1989
57. Koike K, Ono S, Sakuma T, et al. Collapse and reexpansion of lungs increase microvascular permeability in sheep. Tohoku J Exp Med 157:19, 1989
57a. Stampley AR, Waldron DR. Reexpansion pulmonary edema after surgery to repair a diaphragmatic hernia in a cat. J Am Vet Med Assoc 203:1699, 1993
57b. Soderstrom SD, Gilson N, Gulbas TI. Fatal reexpansion pulmonary edema in a kitten following surgical correction of pectus excavatum. J Am Anim Hosp Assoc 31:133, 1995
58. Kerr LY. Pulmonary edema secondary to upper airway obstruction in the dog: A review of nine cases. J Am Anim Hosp Assoc 25:207, 1989
59. Cascade PN, Alexander GD, Mackie DS. Negative pressure pulmonary edema after endotracheal intubation. Radiology 186:671, 1993
60. Younker D, Meadors C, Covelar L. Postobstruction pulmonary edema. Chest 95:687, 1989
61. Guyton AC, Lindsey AW. Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. Circ Res 7:649, 1959
62. Modell JH. Drowning. *In* Staub NC, Taylor AE (eds): Edema. New York, Raven Press, 1984, p 679
63. Cohen DS, Matthay MA, Cogan MG, et al. Pulmonary edema associated with salt water near-drowning: New insights. Am Rev Respir Dis 146:794, 1992
64. Ayres SM: Mechanisms and consequences of pulmonary edema: Cardiac lung, shock lung, and principles of ventilatory therapy in adult respiratory distress syndrome. Am Heart J 103:97, 1982
65. Velazquez M, Schuster DP. Perfusion redistribution after alveolar flooding: Vasoconstriction vs. vascular compression. J Appl Physiol 70:600, 1991
66. Sasaki F, Ishizaki T, Mifune J, et al. Bronchial hyperresponsiveness in patients with chronic congestive heart failure. Chest 97:534, 1990
67. Kappagoda CT, Ravi K, Teo KK. Effect of pulmonary

venous congestion on respiratory rate in dogs. J Physiol Lond 408:115, 1989
68. Oliven A, Kelsen SG. Inspiratory muscle activity during pulmonary edema in anesthetized dogs. Respir Physiol 89:287, 1992
69. Ravi K, Kappagoda CT. Responses of pulmonary C-fibre and rapidly adapting receptor afferents to pulmonary congestion and edema in dogs. Can J Physiol Pharmacol 70:68, 1992
70. Hargreaves M, Ravi K, Kappagoda CT. Responses of slowly and rapidly adapting receptors in the airways of rabbits to changes in the Starling forces. J Physiol Lond 432:81, 1991
71. Domino KB, Lu Y, Eisenstein BL, et al. Hypocapnia worsens arterial blood oxygenation and increases VA/Q heterogeneity in canine pulmonary edema. Anesthesiology 78:91, 1993
72. Suter PF. Thoracic Radiography. Wettswil, Switzerland, PF Suter, 1984
73. David LE. Management of acute pulmonary edema. J Am Vet Med Assoc 175:97, 1979
74. Ware WA. Diagnostic tests for the cardiovascular system. *In* Nelson RW, Couto CG (eds): Essentials of Small Animal Internal Medicine. St Louis, Mosby–Year Book, 1992, p 27
74a. Parent C, King LG, Walker LM, et al. Clinical and clinicopathologic findings in dogs with acute respiratory distress syndrome: 19 cases (1985–1993). J Am Vet Med Assoc 208:1419, 1996
75. Lord PF. Neurogenic pulmonary edema in the dog. J Am Anim Hosp Assoc 11:778, 1975
76. Hamlin RL. Radiographic diagnosis of heart disease in dogs. J Am Vet Med Assoc 137:458, 1960
76a. Parent C, King LG, VanWinkle TJ, et al. Respiratory function and treatment in dogs with acute respiratory distress syndrome: 19 cases (1985–1993). J Am Vet Med Assoc 208:1428, 1996
77. Wickerts CJ, Berg B, Blomqvist H. Influence of positive end-expiratory pressure on extravascular lung water during the formation of experimental hydrostatic pulmonary oedema. Acta Anaesthesiol Scand 36:309, 1992
78. Hawkins EC. Ancillary therapy: Oxygen supplementation and ventilation. *In* Nelson RW, Couto CG (eds): Essentials of Small Animal Internal Medicine. St Louis, Mosby–Year Book, 1992, p 250
79. Moon PF, Concannon KT. Mechanical ventilation. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 98
80. Court MH. Respiratory support of the critically ill small animal patient. *In* Murtaugh RJ, Kaplan PM (eds): Veterinary Emergency and Critical Care Medicine. St Louis, Mosby–Year Book, 1992, p 575
81. Dreyfuss D, Soler P, Saumon G. Spontaneous resolution of pulmonary edema caused by short periods of cyclic overinflation. J Appl Physiol 72:2081, 1992
82. Parker JC, Hernandez LA, Longnecker GL, et al. Lung edema caused by high peak inspiratory pressures in dogs: Role of increased microvascular filtration pressure and permeability. Am Rev Respir Dis 142:321, 1990
83. Wickerts CJ, Blomqvist H, Berg B, et al. Furosemide when used in combination with positive end-expiratory pressure facilitates the resorption of extravascular lung water in experimental hydrostatic pulmonary oedema. Acta Anaesthesiol Scand 35:776, 1991
84. Ali J, Wood LDH. Pulmonary vascular effects of furosemide on gas exchange in pulmonary edema. J Appl Physiol Respir Environ Exer Physiol 57:160, 1984
84a. Fox PR. Current uses and hazards of diuretic therapy. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 668
84b. Supinski G, DiMarco A, Dibner-Dunlap M. Alterations in diaphragm strength and fatigability in congestive heart failure. J Appl Physiol 76:2707, 1994
85. Kittleson MD, Johnson LE, Oliver NB. Acute hemodynamic effects of hydralazine in dogs with chronic mitral regurgitation. J Am Vet Med Assoc 187:258, 1985
85a. Susini G, Zucchetti M, Bortone F, et al. Isolated ultrafiltration in cardiogenic pulmonary edema. Crit Care Med 18:14, 1990
86. Hsu K, Wang D, Li MH, et al. Dimethylthiourea ameliorates acute lung injury induced by phorbol myristate acetate in dogs. Crit Care Med 20:823, 1992
87. Hocking D, Ferro TJ, Johnson A. Dextran sulfate and heparin sulfate inhibit platelet-activating factor-induced pulmonary edema. J Appl Physiol 72:179, 1992
88. Hocking DC, Ferro TJ, Johnson A. Dextran sulfate inhibits PMN-dependent hydrostatic pulmonary edema induced by tumor necrosis factor. J Appl Physiol 70:1121, 1991
89. Prewitt RM, McCarthy J, Wood LDH. Treatment of acute low pressure pulmonary edema in dogs. J Clin Invest 67:409, 1981
90. Morgan RV. Respiratory emergencies. Part I. Compend Contin Educ 5:228, 1983
91. Olivier NB. Pulmonary edema. Vet Clin North Am 15:1011, 1985

14

Pathophysiology and Monitoring of Shock

WILLIAM C. SHOEMAKER

SHOCK, HYPOVOLEMIA, AND LOW-FLOW STATES

THE TRADITIONAL APPROACH

The cardiovascular and pulmonary systems are normally closely integrated to provide tissues with an adequate oxygen supply. These systems function to support metabolism in the normal steady state, as well as during rapidly changing metabolic conditions associated with severe illness. To maintain homeostasis, they must provide oxygen and oxidative substrates to meet tissue metabolic requirements. Critically ill patients usually have compromised circulatory and pulmonary function, which affects oxygen demand and delivery.[1, 2]

Classically, most shock states have been described in terms of hypotension, low blood flow, and high peripheral resistance (chapter 15). It has become evident, however, that inadequate tissue perfusion, not low cardiac output, is the major problem in hemorrhagic, postoperative, traumatic, and septic shock states. In shock, critical illness reduces tissue perfusion, resulting in physiologic states that are inadequate to sustain metabolic requirements. The acutely ill patient with circulatory dysfunction or shock experiences low or unevenly distributed blood flow resulting from hypovolemia, uneven vasoconstriction, and capillary leak. Circulatory disorders have been traditionally evaluated by comparing patient hemodynamic variables against published normal values. However, for optimal clinical evaluation and therapy, this approach often produces poor results.

CLINICAL ASSESSMENT

PHYSICAL EXAMINATION AND PATIENT MONITORING

Shock is a syndrome, not a disease. It is clinically characterized by variable subjective and nonspecific clinical signs (e.g., cold, clammy skin; mucous membrane pallor; weak, thready femoral arterial pulse; unstable vital signs; and reduced level of consciousness). These signs represent the secondary effects of shock, not the principal cause or pathophysiologic mechanism. Unfortunately, subjective signs are commonly used to diagnose shock, to evaluate changes in the clinical status, to assess effects of therapy, and to formulate prognosis. The related lack of objectivity and accuracy is a major

deterrent to a successful outcome. For example, hypotension and oliguria are early and readily detectable manifestations of shock. If these changes alone are used as the therapeutic end-points, treatment with crystalloids and vasopressors may restore blood pressure and urine output to near normal, but underlying deficits in tissue perfusion may remain unnoticed until multiple organ failure occurs.

Similarly, noninvasive monitoring is usually applied to superficial or isolated changes caused by shock, such as blood pressure, heart rate, and the electrocardiogram (ECG). Conventional approaches to shock management have frequently considered each monitored parameter as an independent variable, applying each of them to diagnosis, evaluation, and therapy. Essentially, this one-at-a-time approach precludes organized, systemic analysis of complex cardiopulmonary interactions that determine efficiency of tissue perfusion and oxygen supply.

CLINICAL PATHOLOGY AND HEMODYNAMIC MEASUREMENTS

Although blood pH, base deficit, anion gap, hematocrit (Hct), and blood lactate levels provide more objective measurements to help evaluate shock patients than do clinical signs alone, they do not directly reflect tissue perfusion and oxygenation. Instead, these clinical pathology values represent secondary organ changes as part of complex interrelationships involving anaerobic metabolism.

Traditional hemodynamic measurements commonly monitored in critical care settings are mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), urine output, and arterial oxygen tension (PaO_2). These variables reflect circulatory failure in the late stages of shock but do not measure adequacy of circulatory function or tissue perfusion in the early stages. For example, in studies of human high-risk postoperative patients, these variables correlated poorly with outcome.[2–6] These and other common measurements were restored to their normal range in 76 percent of the nonsurvivors as well as in 75 percent of the survivors, indicating their lack of reliability as outcome predictors.[5–7]

CHANGING CONCEPTS OF SHOCK: CLINICAL IMPLICATIONS

PATHOPHYSIOLOGIC TIME RELATIONSHIPS IN SHOCK

Shock is a labile condition—not static. To understand its pathogenesis, sequential patterns of circulatory changes must be recognized. This begins with the baseline normal state, evolves to reduced tissue oxygenation and subsequent compensatory hyperdynamic states, and ends, finally, in a terminal stage. Physiologic patterns have been demonstrated in survivors compared with patients who die in the late or preterminal stage, although there have been few studies identifying significant differences between groups in early temporal patterns.

The marked variability in circulatory conditions—especially as they relate to metabolic and tissue needs—is clinically important when utilizing hemodynamic and monitoring parameters to decide the type of therapy and timing of certain interventions. An important related issue involves the clinical application of published hemodynamic and oxygen transport variables. These are generally compiled from data collected in critical diseases and are described as mean values ($\pm$ SD or $\pm$ SEM) for each individual variable. One must bear in mind that these values are generally published in tables without regard to temporal relationship to the stage of shock; that is, data throughout the disease course are usually listed as though they occurred consistently, or were representative of a condition when tested at any single point in time. In reality, however, temporal factors vary widely in the development, progression, and resolution of critical illnesses. Thus, the use of mean values and parameters obscures trends in the dynamic process of circulatory failure.

When temporal patterns are taken into account, however, low or inadequate blood flow is frequently observed as an early event antecedent to subsequent hyperdynamic states, tissue hypoxia, vital organ failure, shock, and death. This is particularly true in hemorrhagic, traumatic, septic, and postoperative shock. Low flow in the intraoperative or immediate postoperative period has been identified as the underlying cause of oxygen debt and subsequent multiple organ failure.[6–9]

HEMODYNAMIC AND OXYGEN TRANSPORT MONITORING

Severe illness increases metabolic rates and tissue requirements for circulatory function.[7] Thus, it is imperative that therapeutic goals and physiologic benchmarks utilize supranormal rather than just normal hemodynamic parameters to guide therapy and management decisions.

A wide range of physiologic assessments, hemodynamic measurements, oxygen transport variables, and blood gas parameters are routinely monitored in human critical care settings (Table 14–1; see also Tables 15–6, 15–7). With increases in monitoring capabilities in many veterinary institutions, these factors are more

TABLE 14–1
Clinical Roles for Hemodynamic Monitoring

Diagnose etiologies
Determine hemodynamic basis of circulatory dysfunction
Assess cardiac and pulmonary function
Evaluate tissue perfusion
Titrate treatments
Achieve optimal physiologic goals
Assess therapeutic effectiveness relative to the preceding parameters

frequently being evaluated. Hemodynamic values have been reported and average ranges for cardiovascular disorders described.[1, 2, 4, 5] These hemodynamic and oxygen transport measurements have proved to be more useful when combined with traditional monitoring.[4–8]

It is easier and more effective to observe, analyze, and treat mild circulatory changes at their earliest appearance when they are more responsive to therapy. Moreover, the interactions of heart, lung, and tissue perfusion are easiest to evaluate in the early periods.

ASSESSMENTS OF TISSUE PERFUSION

To be effective, the circulatory system must perfuse tissues with sufficient amounts of oxygenated blood to sustain body metabolism. Tissue perfusion has conventionally been inferred from the subjective signs and symptoms of shock, but not specifically measured. Recently, the most important application of invasive monitoring has been related to quantitative measurements of tissue perfusion and tissue oxygenation by evaluation of temporal changes of oxygen delivery (DO_2) and oxygen consumption (VO_2).

OXYGEN TRANSPORT. Evaluation of the bulk movement of oxygen is a useful measure of tissue perfusion because (a) oxygen is easily measured in arterial and mixed venous blood, (b) it is associated with a large arteriovenous gradient, (c) it is related to overall tissue perfusion and clinical outcome, and (d) cellular oxygen uptake is a measure of overall body metabolism. Reduced tissue oxygenation is the major functional impairment of hemorrhagic, traumatic, septic, and postoperative shock.

Overall measurement of peripheral circulation and tissue perfusion may be quantitatively evaluated by *oxygen delivery* (DO_2), which is the product of cardiac output and arterial content (see Fig. 15–1). Similarly, overall body metabolism may be evaluated by *oxygen consumption* (VO_2), which is the product of cardiac output and the arteriovenous O_2 difference [$C(a-v)O_2$]. The oxygen contents of arterial and mixed venous blood are the products of hemoglobin concentration, the percent hemoglobin saturation, and a constant (1.36) that represents the volume of oxygen carried by each gram of saturated hemoglobin, plus a small amount of oxygen dissolved in plasma ($0.0031 \times PaO_2$).*

Oxygen delivery (i.e., the amount of oxygen delivered to the tissues per minute) is the primary role of the circulatory system. As such, DO_2 reflects the overall circulatory function to peripheral tissues. Increases above the normal range represent compensation. Spontaneous increases in DO_2 in the face of trauma, infection, and other forms of stress represent compensatory responses to increased tissue demands. The increase in cardiac index and DO_2 in response to a standard fluid volume load is also an indirect measure of the circulation's capacity to compensate. Failure of DO_2 to increase with colloid fluid challenge or after stimulation with an inotropic agent such as dobutamine may indicate limited circulatory reserve capacity.

The temporal pattern of DO_2 change is more informative than a single set of measurements.[4] For example, after evaluating a series of high-risk human surgical procedures, survivors generally displayed increased DO_2, VO_2, and cardiac index compared with nonsurvivors in the postoperative period (Fig. 14–1).

The rate of oxygen consumption (VO_2) measures overall body metabolism and represents the total of all oxidative metabolic reactions. The VO_2 may be limited by a progressively decreasing rate of oxygen delivery (DO_2), the "supply side" of the equation. While DO_2/VO_2 relationships have been demonstrated in experimental laboratory studies, the patterns are not always as obvious in clinical conditions, when many other problems may contribute.[10, 11]

EARLY HEMODYNAMIC AND OXYGEN TRANSPORT PATTERNS IN SHOCK

High-risk surgical patients may be used as a model for shock because time relationships can be precisely determined (see Fig. 14–1).[4] In clinical studies, the time-related patterns exhibited by nonsurvivors consisted of reduced blood flow and oxygen transport in the intraoperative and immediate postoperative periods. By contrast, survivors had fewer circulatory deficits and had improved blood flow and oxygen transport variables in the early postoperative period. Compared with the nonsurvivors, the survivors had (a) greater increases in cardiac index and flow-related variables, with lower central venous pressures and pulmonary capillary wedge pressures; (b) less pulmonary vasoconstriction; (c) greater increases in DO_2 and VO_2, with lower oxygen extraction rates and normal blood gases; (d) greater hematocrit, blood volume, and red cell mass, and (e) less pulmonary shunting (Qsp/Qt).[4–6]

*PaO_2, arterial oxygen tension.

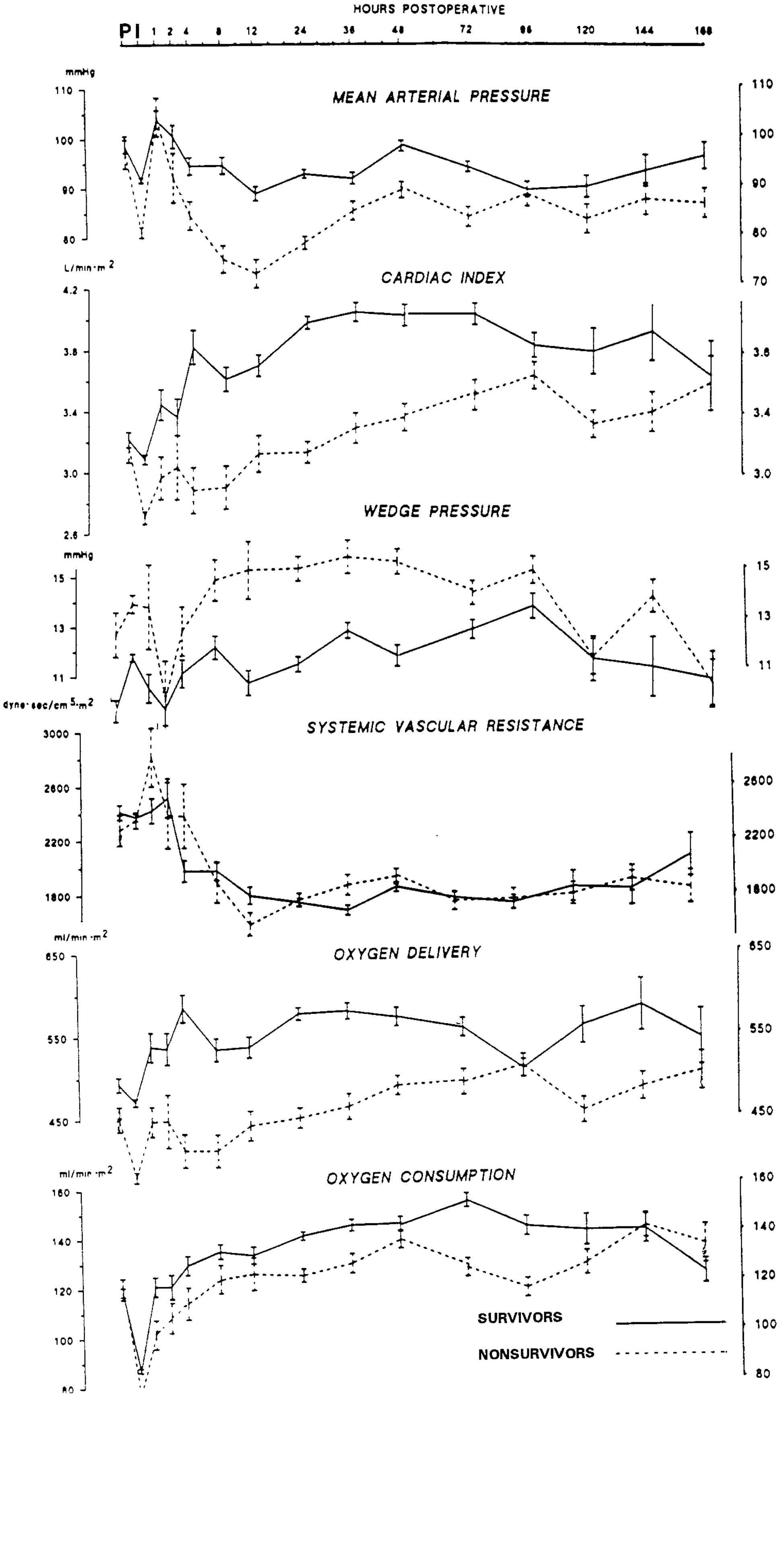


FIGURE 14-1

Temporal patterns of mean arterial pressure, cardiac index, pulmonary artery occlusion (wedge pressure), systemic vascular resistance index, oxygen delivery, and oxygen consumption obtained preoperatively (**P**), intraoperatively (**I**), and at successive time periods postoperatively in a series of survivors and nonsurvivors with organ failure. *Solid lines* denote survivor patterns; *dotted lines* denote nonsurvivor patterns. Data represent mean values ± SEM (*vertical bars*). Survivors had trends of significantly greater cardiac index, oxygen delivery, and oxygen consumption than nonsurvivors. (Redrawn from Shoemaker WC, Appel PA, Kram HB. Hemodynamic and oxygen transport responses in survivors and nonsurvivors of high-risk surgery. Crit Care Med 21:977-990, 1993, with permission.)

Preoperative patients with sepsis, severe stress, accidental injury, and advanced cirrhosis often had high preoperative baseline cardiac index (CI) values.[6] In the postoperative survivors, there were increases over their own baseline values in cardiac index, DO_2, and VO_2 but minimal changes in other hemodynamic variables. Nonsurvivors had little or no increases in cardiac index, DO_2, and VO_2 despite higher central venous pressure and pulmonary artery wedge pressure.

Critically ill patients with congestive heart failure (CHF) or hypovolemic shock usually had preoperative hypotension, high pulmonary artery wedge pressures, and reduced CI, DO_2, and VO_2. However, in the early postoperative period the average CI, DO_2, and VO_2 values of survivors were appreciably higher than those of the nonsurvivors.[6]

OXYGEN DELIVERY AND CONSUMPTION RELATIONSHIPS

The patterns of DO_2 and VO_2 vary in the early compensated states of acute circulatory failure independent of cause. Characteristically, the hemorrhagic and cardiac shock patients have greatly reduced DO_2 with only moderately reduced VO_2, because of increased oxygen extraction. Septic, postoperative, and trauma patients have increased DO_2 and VO_2 in their early compensated states. The combination of sepsis with accidental or surgical trauma increases metabolic demands, as shown by the further increases in VO_2. These data suggest that circulatory function increases when possible to compensate for increased body metabolism. When increases in DO_2 are limited by hypovolemia or reduced cardiac function, an increased oxygen extraction ratio is the principal compensatory response.

ESTIMATION OF OXYGEN DEBT

The degree and duration of tissue hypoxia may be estimated as the net cumulative deficit of oxygen consumption (VO_2). Guyton and colleagues[12, 13] measured VO_2 in dogs subjected to hemorrhage. When the net accumulated O_2 debt was less than 100 ml/kg, all dogs survived. In contrast, when the O_2 debt was greater than 140 ml/kg, all died; the halfway point where 50 percent lived was 120 ml/kg. Other methods have been developed to assess high-risk human surgical patients.[9]

OUTCOME PREDICTION

The common denominator of shock and the major determinant of outcome is inadequate tissue oxygen delivery (DO_2) and consumption (VO_2) with related oxygen debt.[1–3, 6, 9] Inadequate VO_2, which is the earliest pathogenic circulatory event, appears at, or before, the initial hypotensive crisis. It leads to oxygen debt that limits body metabolism and increases mortality and morbidity.

Inadequate oxygen consumption may result from (a) low blood flow from cardiogenic or hemorrhagic shock, (b) maldistribution of blood flow due to uneven microcirculatory vasoconstriction, and (c) increased tissue metabolism from sepsis, trauma, stress, or other disorders. Low flow or uneven (i.e., maldistributed) flow successively leads to tissue hypoxia, organ dysfunction, organ failure, and death.[5, 8–25] In acute illness, oxygen debt may occur from increased tissue metabolic demand or reduced oxygen supply. Decreased oxygen delivery occurs in cardiac insufficiency or failure, hypoxemia, respiratory failure, trauma, hemorrhage, dehydration, cardiopulmonary arrest, and other acute circulatory catastrophes.

Tissue hypoxia precipitates or triggers a number of metabolic responses (chapter 15). These include the arachidonic acid cascades to form thromboxane, prostaglandins, and leukotrienes; production of histamine, other amines, and serotonin; complement system activation; tumor necrosis factor (TNF) and cytokine production; bacterial antigenemia; and formation of oxygen free radicals. These mediators are thought to initiate or intensify organ failure.

THERAPEUTIC GOALS

Studies have demonstrated a direct relationship between patterns of cardiac index, DO_2, VO_2, oxygen debt, organ failure, and death.[1, 9–11, 26, 28] These clinical trials showed improved survival, reduced organ failure, and decreased treatment costs when supranormal values for cardiac index, DO_2, and VO_2 were used as therapeutic goals in the first 8 to 12 hours after high-risk surgery.[5–7, 10, 14–23] However, when optimal therapy is delayed until after organ failure occurs, it is not effective.

Multicomponent monitoring provides insight into the markedly different physiologic changes occurring over time in critical patients. Early abnormal changes ("monitored events") in cardiac, pulmonary, and tissue perfusion are utilized to guide therapy by some clinicians. These have been defined in human studies as a sudden decrease (> 20%) in cardiac index, or reductions of cardiac index less than 2.5 L/min/m^2; decreased SaO_2* by pulse oximetry less than 90 percent, transcutaneous oxygen tension ($P_{tc}O_2$) to less

*SaO_2, arterial oxygen saturation.

than 50 torr, and $P_{tc}O_2/PaO_2$ to less than 0.60.[26] These noninvasive monitoring systems may be used to evaluate serial functional changes of cardiac, respiratory, and peripheral tissue function.[4] Cardiac index identifies changes in cardiac function. Blood gases measured by conventional blood gas analysis and by pulse oximeter reflect pulmonary function. The $P_{tc}O_2$ and $P_{tc}O_2/PaO_2$ index indicates tissue perfusion, as do DO_2 and VO_2.

In one study, use of these parameters identified 636 events in 247 high-risk surgical patients just before, during, or immediately after high-risk surgery.[26] At the time of the baseline evaluation, about three fourths of the perioperative events recorded normal or increased cardiac, respiratory, and peripheral perfusion, but about one fourth had reduced function in one or more of these areas. At the nadir, cardiac index was decreased in about two thirds of the events and perfusion was decreased in over half, but PaO_2 was reduced in only one quarter. Recovery was associated with improved blood flow in about two thirds of the events and improved perfusion in over half, but improvement in PaO_2 occurred in less than 1 in 5.

OPTIMIZING PHYSIOLOGIC VARIABLES FOR SHOCK MANAGEMENT

Targeting supranormal physiologic parameters should be a major goal in shock management.[24] The concept of achieving supranormal values has been supported by many investigators.[10, 12, 13, 15, 18–21, 24, 27] Data from human studies showed no significant differences between the mortality of patients managed with a CVP catheter and those with pulmonary artery catheters using normal values as therapeutic goals. By contrast, when pulmonary artery catheter monitoring was used to guide therapy to achieve supranormal physiologic goals (cardiac index, DO_2, and VO_2), morbidity and mortality were significantly reduced.[6, 15–25] Thus, therapeutic interventions can be guided by intensive patient monitoring to allow treatment modifications as necessary (see Table 14–1; see also Tables 15–6, 15–7). Similarly, documentation of relatively normal or low physiologic oxygen transport and hemodynamic values could serve as an early warning for adverse outcome.[1, 2, 4, 12]

TITRATION OF THERAPY TO ACHIEVE OPTIMAL GOALS

Increasing circulatory function to achieve supranormal oxygen transport values helps maximize oxygen delivery. For example, if therapy increases oxygen delivery (DO_2) by 50 to 100 ml/min/m^2, and oxygen consumption (VO_2) also increases by 15 to 25 ml/min/m^2, "supply-dependent" VO_2 may be assumed, and further therapy should be considered. By contrast, if no increase in VO_2 results from significantly increased DO_2, "supply-independent" VO_2 may be assumed; this suggests that the oxygen debt has been corrected, or the microcirculatory defect is irreversible or uncorrected with the given therapy and dose.[11]

Therapeutic algorithms have been successfully applied for initial therapy in human critical care. These are then modified as required for patient age, various specific diagnostic and high-risk categories, hyperdynamic states (trauma, stress, sepsis, recent surgery), hypodynamic states (hemorrhage, hypovolemia, and cardiogenic problems), specific organ failures (respiratory, renal, hepatic, cardiac, central nervous system), and postoperative complications (sepsis, septic shock, disseminated intravascular coagulation, and nutritional failure).[4, 28] The objective is to minimize the degree and duration of tissue hypoxia. Guidelines for hemodynamic and blood gas monitoring are listed (see Tables 15–6, 15–7).

FLUIDS AND TRANSFUSIONS. Hemodynamic and oxygen transport responses to fluid therapy are roughly proportional to their success in expanding plasma volume. Colloids expand plasma volume and improve hemodynamics and oxygen transport, whereas crystalloids largely expand interstitial volume.[10, 11] Crystalloid infusions therefore require very large volumes. For the critically ill, high-risk, noncardiac failure patient, vigorous fluid loading without exceeding a pulmonary wedge pressure of 20 mmHg is the first and most important maneuver to achieve optimal volume expansion. The use of colloids, dextrans, and hydroxyethyl starch is discussed (see Tables 15–4, 15–5). Critically ill patients may also require transfusions to maintain hematocrit levels sufficient to provide optimal oxygen delivery.

INOTROPIC AGENTS. After fluid administration has been maximized, inotropes may be necessary in some patients to maintain or increase forward stroke volume (see Table 15–4). Dobutamine is generally the agent of choice. It improves cardiac contractility by stimulating myocardial β_1-adrenergic receptors and by relaxing previously vasoconstricted metarterioles (β_2-adrenergic effects), thus improving microcirculatory flow and tissue oxygenation.[11, 15] The initial dose (2 to 5 μg/kg/min) should be increased as required to reach optimal goals. Hypotension may occur if hypovolemia has not been previously corrected by adequate fluid therapy.

VASODILATORS. Vasodilators such as nitroprusside, nitroglycerin, hydralazine, and labetalol are generally used to treat cardiogenic pulmonary edema (pulmonary artery wedge pressure > 20 mmHg) (see Table 15–8). Blood pressure monitoring is necessary to detect and prevent hypotension.

VASOPRESSORS. Dopamine, norepinephrine, or epinephrine can be used to correct hypotension if fluid resuscitation has not adequately restored blood flow (see Table 15–4). However, vasoconstriction may reduce microcirculation and worsen tissue perfusion by α_1-adrenergic stimulation of smooth muscle in metarterioles.

REFERENCES

1. Weissman C, Kemper M, Harding J. Response of critically ill patients to increased oxygen demand: Hemodynamic subsets. Crit Care Med 22:1809, 1994
2. Shoemaker WC. Monitoring and management of acute circulatory problems. Am J Crit Care 1:38, 1992
3. Cournand A, Riley RL, Bradley SE, et al. Studies of the circulation in clinical shock. Surgery 13:964, 1943
4. Shoemaker WC, Appel PL, Kram HB. Hemodynamic and oxygen transport responses in survivors and nonsurvivors of high-risk surgery. Crit Care Med 21:977, 1993
5. Bland RD, Shoemaker WC, et al. Probability of survival as a prognostic and severity of illness score in critically ill surgical patients. Crit Care Med 13:91, 1985
6. Shoemaker WC, Appel PL, Kram HB, et al. Prospective trial of supranormal values of survivors as therapeutic goals in patients. Chest 94:1176, 1988
7. Bland R, Shoemaker WC, Shabot MM. Physiologic monitoring goals for the critically ill patient. Surg Gynecol Obstet 147:833, 1978
8. Forrester JS, Diamond G, Chatterjee K, et al. Medical therapy of myocardial infarction by application of hemodynamic subsets. N Engl J Med 295:1356, 1976
9. Shoemaker WC, Appel PL, Kram HB. Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. Crit Care Med 16:1123, 1988
10. Shoemaker WC. Diagnosis and treatment of the shock syndromes. *In* Shoemaker WC, Thompson WL, Holbrook PR (eds): Textbook of Critical Care. 3rd ed. Philadelphia, WB Saunders, 1995, p 85
11. Shoemaker WC, Appel PL, Kram HB. Oxygen transport measurements to evaluate tissue perfusion and titrate therapy: Dobutamine and dopamine effects. Crit Care Med 19:572, 1991
12. Crowell JW, Smith EE. Oxygen deficit and irreversible hemorrhagic shock. Am J Physiol 106:313, 1964
13. Guyton AC, Crowell JW. Dynamics of the heart in shock. Fed Proc 10:51, 1961
14. Hankeln K, Senker R, Schwarten JM, et al. Evaluation of prognostic indices based on hemodynamic and oxygen transport variables in shock patients with ARDS. Crit Care Med 15:1, 1987
15. Edwards JD, Brown GC, Nightingale P, et al. Use of survivors' cardiorespiratory values as therapeutic goals in septic shock. Crit Care Med 17:1098, 1989
16. Tuchschmidt J, Fried J, Astiz M, et al. Evaluation of cardiac output and oxygen delivery improves outcome in septic shock. Chest 102:216, 1992
17. Creamer J, Edwards JD, Nightingale P. Hemodynamic and oxygen transport variables in cardiogenic shock following acute myocardial infarction and their responses to treatment. Am J Cardiol 55:1297, 1990
18. Berlauk JF, Abrams JH, Gilmour IJ, et al. Preoperative optimization of cardiovascular hemodynamics improves outcome in peripheral vascular surgery. Ann Surg 214:289, 1991
19. Hayes MA, Yan EHA, Timins AC, et al. Response of critically ill patients to treatment aimed at achieving supranormal oxygen delivery and consumption in relation to outcome. Chest 103:886, 1993
20. Bishop MH, Shoemaker WC, Appel PL, et al. Relationship between supranormal circulatory values, time delays, and outcome in severely traumatized patients. Crit Care Med 21:56, 1993
21. Gilbert EM, Haupt MT, Mandanas RT, et al. The effect of fluid loading, blood transfusion, and catecholamine infusion on oxygen delivery and consumption in patients with sepsis. Am Rev Respir Dis 134:875, 1986
22. Boyd O, Grounds M, Bennett D. Preoperative increase of oxygen delivery reduces mortality in high-risk surgical patients. JAMA 270:2699, 1993
23. Astiz ME, Rackow EC, Falk JL, et al. Oxygen delivery and consumption in patients with hyperdynamic septic shock. Crit Care Med 15:26, 1987
24. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 333:1025, 1995
25. Moore FA, Haemel JB, Moore EE, et al. Incommensurate oxygen consumption in response to maximal oxygen availability predicts post injury organ failure. J Trauma 33:58, 1992
26. Shoemaker WC, Appel PL, Kram HB. Incidence, physiologic description, compensatory mechanisms, and therapeutic implications of monitored events. Crit Care Med 17:1277, 1989
27. Scalea TM, Simon HM, Duncan AO, et al. Geriatric blunt multiple trauma: Improved survival with early invasive monitoring. J Trauma 30:129, 1990
28. Shoemaker WC, Patil R, Appel PL, et al. Hemodynamic and oxygen transport patterns for outcome prediction, therapeutic goals and clinical algorithms: Feasibility of artificial intelligence to customize algorithms. Chest 102:617S, 1992

15

Treatment of Shock

STEVEN C. HASKINS

"Shock" is a syndrome—not a disease. It is associated with acute reduction in effective blood flow, resulting in failure to maintain transport and delivery of vital substrates to sustain organ function.[1,2]

DEFINITION. In this chapter, *shock* is defined as inadequate cellular energy production. Thus, the term can be applied to any progressive disease or process that leads to disruption of cellular and organ function and, ultimately, death. Hypoperfusion is a key concept in the recognition and understanding of shock.

To describe an animal as being "in shock" says very little other than that the animal is "really sick." Thus, the term "shock" should always be preceded by a descriptive adjective (e.g., hypovolemic, cardiogenic, septic, and so on) to help characterize the underlying pathophysiology. The word "shock" is applied when clinical signs indicate cardiovascular collapse, mental obtundation, and other signs related to reduced systemic blood flow.

CLINICAL CATEGORIES OF SHOCK

For clinical purposes, it is useful to categorize shock states based on the mechanism or primary cause of circulatory failure (Table 15–1). These groupings are often somewhat arbitrary, share overlapping mechanisms, and serve only to illustrate the multiple avenues by which organ dysfunction may develop. An animal may have more than one type of shock, and the characteristics of circulatory disturbance may change with time or therapy (see Fig. 33–8).

CARDIOGENIC SHOCK

Cardiogenic shock is a syndrome in which inadequate cardiac output causes insufficient delivery of oxygen to tissues, resulting in inability of the heart to meet resting tissue metabolic demands.[3] Etiologies include primary or secondary dilated cardiomyopathy; pericardial tamponade; myocardial toxins (e.g., Adriamycin toxicity); and drugs that depress myocardial function (general anesthetics, large doses of β-adrenergic blockers).[4] Congestive heart failure, ischemic injury and necrosis, or metabolic derangement may progress to cardiogenic shock. Without therapy, deterioration is relentless. Sympathetic nervous system and renal-neurohumoral activation results in a spiraling decline of cardiovascular function.

Hemodynamic features of cardiogenic shock include low systolic (<80 mmHg), or mean (<60 mmHg) blood pressure; elevated arteriovenous

TABLE 15-1
Clinical Classification of Shock: Mechanism or Primary Cause

Shock Classification	Primary Mechanism	Examples
Cardiogenic	Poor contractility	Dilated cardiomyopathy Toxins/drugs Myocardial infarction Pericardial tamponade
Distributive	Vasomotor dysfunction Hypotension (expanded venous capacitance) High or normal resistance	Arteriovenous shunting Hypodynamic late septic shock
Hypoxemic	Lack of oxygen	Anemia Hypoxemia
Metabolic	Inability to utilize energy substrates	Sepsis Cyanide poisoning Heat stroke Hypoglycemia
Obstructive	Inadequate cardiac preload	Pericardial tamponade Restrictive pericarditis Intracardiac masses
Hypovolemic	Inadequate circulating blood volume	Dehydration (any cause), hypoproteinemia Blood loss
Septic	Bacteremia Endotoxemia	Sepsis

oxygen difference; depressed cardiac index (cardiac output related to body weight); elevated central venous (>10 mmH_2O) and pulmonary capillary wedge pressure (>15 mmHg).[5]

Low-flow states resulting from hypovolemia may have hemodynamic profiles similar to cardiogenic shock with an important exception: with cardiogenic shock, there are elevated ventricular filling pressures (i.e., increased left-sided heart preload suggested by pulmonary artery wedge pressure >15 mmHg, and elevated right-sided heart preload suggested by jugular venous distention and increased central venous pressure generally >10 cm H_2O).

Clinical features of myocardial failure include inadequate tissue perfusion, often coupled with gallop rhythms, cardiac murmurs, electrocardiographic (ECG) abnormalities (arrhythmias, cardiac chamber enlargement patterns), and thoracic radiographic changes (severe cardiomegaly, effusions, congestion). When cardiogenic shock is suspected, an ECG should be obtained immediately, because evidence of significant abnormalities may focus attention toward the heart. Echocardiography (chapter 8) provides a rapid, noninvasive, and accurate test to assess cardiac structure and function. Radiographs are essential for diagnosis and to plan treatment. Specific therapies are reviewed in chapters 25 through 29.

DISTRIBUTIVE SHOCK

This category encompasses a potpourri of conditions. It represents severe alteration in distribution of blood flow—without critical decrease of intravascular volume, cardiac function, or obstruction to blood flow.[6] Distributive shock may result from decreased arterial resistance caused by inflammatory vasodilation, arteriovenous shunting, or increased venous capacitance as in septic shock. Arteriovenous shunts reduce net cardiac output and tissue blood flow. Severe trauma may cause signs similar to those of hypovolemic shock (even though there is no evidence of blood loss) due to maldistribution of available blood volume.[7] Cardiac output may be increased but is inadequate to maintain normal tissue requirements. Peripheral vascular resistance is reduced, and hypotension is present.

HYPOVOLEMIC SHOCK

Hypovolemia is the most common cause of reduced systemic blood flow and may result from whole blood or plasma loss, hypoproteinemia, increased vascular permeability, or any cause of dehydration. Hypovolemia is considered to be a form of distributive shock by some because it is normally associated with compensatory peripheral vasoconstriction, which interferes with peripheral (visceral organ) perfusion.

OBSTRUCTIVE SHOCK

Obstruction to cardiac filling reduces cardiac preload and leads to reduced cardiac output. Impedance to cardiac filling most commonly results from pericardial tamponade (chapter 29). Other disorders include large space-occupying masses in the atria, ventricles, or cava; torsion of spleen, stomach, or intestines; masses impinging on major vessels; and severe embolization.

HYPOXEMIC SHOCK

Hypoxemic shock implies that tissues are being perfused (to differentiate it from distributive shock), but tissue oxygenation is severely impaired. The two common examples of hypoxic shock include anemia (low oxygen content) and hypoxemia (low partial pressure of oxygen or low hemoglobin saturation due to pulmonary pathology). Methemoglobinemia (oxidized, ferric hemoglobin) and carboxyhemoglobin (carbon monoxide poisoning) decrease the oxygen-carrying capacity of hemoglobin.

METABOLIC SHOCK

Neurohormonal or intracellular reflexes may interfere with cellular energy production even though tis-

sues are being adequately perfused and oxygenated. Metabolic responses may be altered in sepsis somewhat differently from the effects of vasoactive intermediates and cell-mediated injury.

A number of conditions can cause metabolic shock. Cyanide intoxication can interfere with mitochondrial cytochromic oxidative phosphorylation. Heat stroke is a form of metabolic shock in which the metabolic rate exceeds the animal's ability to deliver energy substrates. Hypoglycemia causes inadequate energy substrate for cerebral metabolism.

SEPTIC SHOCK

This complex syndrome causes multiple and disparate clinical abnormalities that are often complicated by signs related to the inciting illness (see Fig. 33–8). The most frequent cause is gram-negative bacteremia.[8] There are multiple risk factors: infectious disorders, debilitating conditions (e.g., trauma, neoplasia, gastroenteritis, burns), immunosuppression (e.g., viruses including feline immunodeficiency virus and feline leukemia virus, glucocorticosteroid therapy, chemotherapy), surgery, and indwelling catheters.[9] Prognosis is usually grave. Septic shock is a form of distributive shock resulting from intravascular bacteria (bacteremia) and/or enterotoxins (heat-labile bacterial toxins primarily from gram-negative bacteria).

Endogenous mediators activated by any systemic condition (Table 15–2) may trigger enzymatic cascades with systemic consequences, including vasodilation, complement system activation, and leukotaxis.[1, 10] These cascades include (1) tumor necrosis factor released from macrophages; (2) platelet-activating factor from macrophages, neutrophils, platelets, and endothelial cells; (3) interleukin-1 and -6 from macrophages and endothelial cells; (4) neutrophil activation with the release of superoxide, proteases, and catalases; (5) eicosanoids (thromboxane and leukotrienes) from cell membranes of macrophages, neutrophils, platelets, and mast cells; and (6) activation of complement (anaphylatoxins C3a and C5a), coagulation, and fibrinolytic cascades.

Early in septic shock, decreased systemic vascular resistance (from mediator-induced vasodilation) results in increased stroke volume and cardiac output, causing a hyperdynamic state. Venous dilation results in venous pooling and decreased cardiac return. Clinical signs include tachypnea, tachycardia, bounding femoral arterial pulses, and red mucous membranes.[6] Later stages result in a hypodynamic state characterized by hypotension, decreased cardiac output, and increased peripheral vascular resistance. With lethal progression, decreased right and left ventricular function and cardiac output occur.[11]

TABLE 15–2
Systemic Stressors Capable of Inducing Systemic Inflammatory Response Syndrome (SIRS) and Multiple Organ Dysfunction Syndrome (MODS)

Sepsis (bacterial, viral, fungal, rickettsial, spirochetal)
Heat stroke
Trauma
Pancreatitis
Uremia
Gastrointestinal ischemic or inflammatory disease
Disseminated cancer
Hypovolemic shock
Autoimmune diseases (AIHA, ITP, SLE*)

*AIHA, autoimmune hemolytic anemia; ITP, immune thrombocytopenic purpura; SLE, systemic lupus erythematosus.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

Once activated, these cascades propagate positive feedback loops to one another that "autoperpetuate" the entire process and cause adverse systemic effects. The clinical and laboratory manifestation of this process is referred to as the *systemic inflammatory response syndrome,* or SIRS (Table 15–3). "Septic" SIRS describes the condition when an infectious cause is detected.

MULTIPLE ORGAN DYSFUNCTION SYNDROME (MODS)

When the systemic inflammatory response syndrome becomes severe or prolonged, organ function deteriorates. This results in the *multiple organ dysfunction syndrome,* or MODS (Table 15–3). When the cause is sepsis (based upon positive blood cultures or fever with leukocytosis), then the term "septic" MODS or septic shock is appropriate.

One must realize that SIRS and MODS represent two stages of a disease continuum. The clinical findings can often overlap, and there is not always a clear clinical distinction between the two. Organ function declines in shock as cell function deteriorates. Myocardial contractility, cardiac output, and oxygen delivery decrease. Inappropriate changes in vasomotor tone occur, resulting in either vasodilation (hypotension) or vasoconstriction (impaired tissue perfusion). Gastrointestinal ulceration and hemorrhage occur. Oliguric or anuric renal failure ensues. Vascular permeability decreases, resulting in hypoproteinemia and hypovolemia. Diffuse, infiltrative pulmonary edema and hypoxemia develop. Anemia, hypoproteinemia, coagulopathies, lactic acidosis, and hypoglycemia are also common features of SIRS and MODS.

Treatment is directed toward restoring tissue perfu-

TABLE 15–3
Clinical Manifestations of Systemic Inflammatory Response Syndrome (SIRS) and Multiple Organ Dysfunction Syndrome (MODS)

	SIRS	MODS
Historical Abnormalities		
Anorexia	+/++	++/+++
Lethargy	+/++	++/+++
Diarrhea (hemorrhagic)		±
Physical Examination		
Clinical depression	+/++	+++
Fever	Y	
Hypothermia		Y
Vasodilation (red mucous membranes; accelerated capillary refill time)	Y	
Vasoconstriction (pale mucous membranes; prolonged capillary refill time)		Y
Heart murmur	Y	±
Arterial pulse quality		
"Bounding"	Y	
Normal or decreased		Y
Tachycardia; arrhythmias	±	Y
Tachypnea; hyperventilation	Y	Y
Petechiae or bleeding	±	±/Y
Clinical Pathology		
Hyperglycemia	±/Y	
Hypoglycemia		±/Y
Leukocytosis (possibly following transient leukopenia; left shift, mild toxic changes)	Y	
Leukopenia or rapid decrease in leukocytes with marked left shift, toxic neutrophils		Y
Coagulation parameters		
Normal to hyperactive	Y	
Hypoactive		Y
Increased liver enzymes (particularly alkaline phosphatase)	Y	Y
Jaundice		±/Y
Hypoalbuminemia	±/Y	±/Y
Azotemia	+/++	+/++/+++
Acidosis (lactic/metabolic)	±	+/++
Hemodynamic Changes		
Cardiac output		
Normal to high	Y	
Low		Y
Arterial blood pressure; central venous pressure		
Normal	+/++	+
Low	+/++/+++	+/++

Y, usually present; ±, possibly present; +/++/+++, mild, moderate, severe.

sion and abolishing systemic infection. Management of SIRS and MODS is primarily directed toward the underlying disease process and secondarily toward systemic manifestations. Each major organ system must be evaluated thoroughly and repeatedly and therapy modified accordingly (Table 15–4).

MANAGEMENT OF SHOCK

The acronym "VIP" is clinically useful to guide initial management of the shock patient. V refers to ventilation (ensure pulmonary O_2 and CO_2 exchange); I to infusion (provide adequate intravascular volume); and P to pumping (support cardiac function).[12] Conventional views have traditionally focused on restoring circulation to "normal" and treating problems associated with organ system failure. Newer views for some types of shock stress attaining objectives of enhanced tissue oxygen delivery and consumption in concert with restoring circulation, cardiac output, and other hemodynamic variables to higher than "normal" values (chapter 14).[13, 14]

VENTILATION

Clinical observation of the thoracic excursion and breathing pattern for adequate chest movement and respiratory distress is enhanced by arterial blood gas analysis to measure acid-base status and ventilation adequacy. Hypoxemia in the absence of hypercapnia and respiratory acidosis indicates the need for increasing inspired oxygen concentration (e.g., oxygen therapy using nasal oxygen delivery). If increasing inspired O_2 fails to reverse hypoxemia (PaO_2 <60 mmHg), or if progressive respiratory acidosis occurs ($PaCO_2$ > 60 mmHg), endotracheal intubation and ventilation (assisted or intermittent) with a volume-controlled respirator may be considered. If decreasing pulmonary compliance or "shock lung" (acute respiratory distress syndrome, or ARDS) develops, PEEP (positive end-expiratory pressure) or CPAP (continuous positive airway pressure) may recruit alveoli and decrease pulmonary arterial venous shunting.[15]

The need for ventilatory support (i.e., PEEP, CPAP) must be balanced with the potential for deleterious effects. Mechanical ventilation increases intrathoracic pressure. This impedes venous cardiac return (preload) and thus cardiac output and oxygen delivery.

INFUSION (FLUID THERAPY)

Restoration of an effective circulatory volume is a first priority in the management of shock and multiple organ dysfunction. Clinical evidence suggesting diminished circulating volume includes (1) a history of excessive fluid or blood loss (vomiting, diarrhea, hemorrhage), (2) signs referable to severe dehydration (decreased skin turgor, tacky oral mucous membranes), (3) signs referable to arterial vasoconstriction (prolonged capillary refill time, cool appendages, an-

TABLE 15–4
Treatment of SIRS and MODS

Restore Effective Circulating Volume
- Crystalloids: 40 to 100 ml/kg IV
- Colloids: 10 to 30 ml/kg IV
- Hypertonic saline: 4–6 ml/kg IV of 7.5% hypertonic saline

Support Cardiovascular Function (myocardial contractility, cardiac output, arterial blood pressure, and oxygen delivery)
- Dopamine (CRI): 1–3 μg/kg/min (dopaminergic activity; increase renal perfusion)
  - 3–5 μg/kg/min (β_1-adrenergic activity; inotropic support)
  - 5–10 μg/kg/min (α-agonist activity; vasopressor)
- Dobutamine (CRI): 2–15 μg/kg/min
- Pressors (CRI):
  - Dopamine: 5–10 μg/kg/min
  - Norepinephrine: 0.1–1 μg/kg/min
- Vasodilators:
  - Hydralazine: 1–3 mg/kg PO bid; especially pulmonary edema from chronic mitral regurgitation
  - Nitroprusside: 1–10 μg/kg/min CRI; cardiogenic pulmonary edema

Optimize Pulmonary Function
- Oxygen: maintain PaO_2 >80 mmHg; SaO_2 >95%
- Positive pressure ventilation
- Positive end-expiratory pressure (PEEP); 5 to 15 cm H_2O

Maintain Blood Oxygen Content
- Red blood cell substitutes (Oxyglobin, see text)
- Transfusion therapy (maintain PCV >25 to 30%)
  - Packed red cells: 11 ml/kg will increase PVC approximately 10%
  - Stored whole blood: 22 ml/kg will increase PCV approximately 10%
  - Maintain PaO_2 (partial pressure of oxygen) >80 mmHg; SaO_2 >95%

Support Colloid Oncotic Pressure (maintain total protein >3.5–4.0 g/dl; Alb >1.5–2.0 g/dl; colloid oncotic pressure >15 mmHg):
- Plasma: 10 ml/kg IV
- Hetastarch: 10–30 ml/kg/day
- Dextrans: 20 ml/kg for 1st 24 hr; 10 ml/kg for 2nd 24 hr
- Whole blood: Dogs, 10–40 ml/kg; cats, 5–20 ml/kg

Maintain Urine Output (1–2 ml/kg/hr)
- Fluids: Maintain CVP approximately 8–10 cm H_2O, mean arterial blood pressure >80 mmHg, and systolic arterial blood pressure >100 mmHg
- Diuretics (mannitol; furosemide; dopamine)

Gastrointestinal Support
- Fluids (as above); enteral nutrition; histamine$_2$-blockers; sucralfate; misoprostil; corticosteroids

Treat Coagulopathies (DIC)
- Heparin
- Fresh plasma: 10 ml/kg IV (repeat until bleeding controlled)
- Cryoprecipitate: 0.5 unit/4.5 kg (repeat until bleeding controlled)

Antimicrobials

Other Therapies
- Glucocorticosteroids
- Glucose
- Sodium bicarbonate
- Nutritional support

CRI, constant rate infusion; PCV, packed cell volume; SaO_2, oxygen percent saturation, arterial; DIC, disseminated intravascular coagulation.

uria), and (4) poor femoral arterial pulse quality, and low central venous and arterial blood pressures. Endpoints of initial fluid administration include decrease or normalization of heart rate, restoration of acceptable femoral arterial pulse quality, and a return of urine output. Restoration of the central venous pressure (CVP) to a high-normal level (8 to 10 cm H_2O) suggests that an adequate volume load is being presented to the heart. Restoration of mean (>60–80 mmHg) systemic blood pressure is important to cerebral and coronary perfusion.

CRYSTALLOIDS

Lactated Ringer's or equivalent solution, having approximately normal extracellular concentrations of sodium, potassium, chloride, and a "bicarbonate-like" anion (bicarbonate, lactate, gluconate, or acetate), is a good fluid with which to begin blood volume restoration therapy. These fluids can be administered rapidly, in large volumes, without causing important changes in major extracellular electrolyte concentrations. Crystalloid fluids may need to be administered in volumes equivalent to half to one, or more, times the animal's estimated blood volume (i.e., 80 to 90 ml/kg for the dog and 50 to 55 ml/kg for the cat). Animals with coexistent pulmonary edema, cerebral edema, or congestive heart failure require close monitoring and attenuation of fluid infusion to assure adequate blood volume restoration without worsening these conditions.

The volume restoration achieved by crystalloid fluids may be fleeting, and if hypotension or vasoconstriction recurs (fluid redistribution or continued bleeding may be the cause), further fluid administration, perhaps in the form of colloids or whole blood, is indicated. Only about 20 percent of a crystalloid fluid remains in the vascular fluid compartment 30 minutes following administration.[16–18] The remainder diffuses across endothelial membranes to be redistributed into the interstitial fluid compartment. Addition of blood or colloid therapy may help sustain vascular fluid volumes.

Excessive hemodilution is a common limitation to crystalloid fluid administration. This is defined as a packed cell volume less than 15 to 25 percent (depending upon the systemic status of the patient; see

later discussion under Integrated Monitoring of Cardiopulmonary Function) or a total protein less than 3.5 g/dl (albumin <1.5 g/dl).

Subcutaneous edema formation during fluid administration may occur with excessive crystalloid therapy. Edema may occur in the face of hypovolemia if the patient is hypoproteinemic or if there is increased vascular permeability. Vascular permeability can be high in septic shock, allowing leakage of even very high molecular colloids.

HYPERTONIC SALINE

In some cases it is difficult to administer sufficient fluid volumes rapidly enough for resuscitation. This is especially true when time is limited by critical status and when large patient size limits rapid infusion of large volumes. Hypertonic saline may be selected to achieve the greatest cardiovascular benefit with the least volume of infused fluids. It improves most cardiovascular parameters and tissue perfusion, and decreases the required volume of subsequent fluids.[19-23] The optimal concentration or dose of hypertonic saline has not been clearly established, but 7.5 percent is the most commonly studied formulation. It may also be administered intraosseous.

One-time intravenous administration of relatively small doses (3 to 5 mg/kg of 2400 milliosmoles [7.5 percent] slowly over 3 to 5 minutes) induces plasma volume expansion. Marked effects on resuscitation in hypovolemia or hemorrhagic shock have been reported.[21-23] The most commonly recommended dose is 4–6 ml/kg over 3 to 5 minutes.

Mechanisms of action are probably more complicated than can be explained only by fluid shifts from the intracellular to extracellular fluid compartments. Additional actions thought to be important include osmoreceptor- and neurohumoral-stimulated effects.[24]

Certain factors limit efficacy of hypertonic saline. As with crystalloids, fluid redistribution from the intravascular to extravascular compartments occurs. Thus, the intravascular volume-expanding qualities and hemodynamic effects of hypertonic saline are short-lived. This may necessitate additional fluid therapy such as colloid, blood component, or crystalloid administration. Deleterious effects of 7.5 percent saline include hypernatremia, hyperchloremia, hyperosmolality, hypokalemia, hypobicarbonatemia, and acidemia. Its use, therefore, is limited to initial resuscitation, and it should not be repeated.

COLLOIDS

Colloid solutions may be more effective than hypertonic saline in restoring blood volume. They are retained to a greater extent within the vascular fluid compartment and therefore exert longer-lasting effects. Use of colloids should be considered (1) when there is lack of response to crystalloid fluid infusion, (2) when edema develops prior to adequate blood volume restoration, and (3) when it is necessary to reduce required crystalloid fluid volume administration. Both hetastarch and dextrans are similarly effective at expanding blood volume.[25] They are approximately 3 to 4 times more effective at restoring blood volume compared to isotonic crystalloids. Infusion of colloids increases colloid oncotic pressure, whereas administration of crystalloid fluids decreases it. Dextran 70 and hetastarch are probably equally efficacious in raising plasma oncotic pressure and volume. A number of colloid solutions are commercially available (Table 15–5).

Synthetic colloids are commercially packaged and are generally iso-osmotic and hyperoncotic. They support plasma colloid oncotic pressure and thus help counteract effects of reduced plasma colloid oncotic pressure associated with hypoproteinemia. If the total protein is low (<3.5 g/dl or albumin <1.5 g/dl), or is likely to be reduced below this level with crystalloid therapy, plasma or a plasma substitute (dextran 70 or hetastarch) may be administered as part of the fluid therapy.

Potential limitations of high doses include increased clotting times resulting from platelet dysfunction and fibrin clot alteration, although these effects may be somewhat less with hetastarch than with dextrans.

HETASTARCH. Hydroxyethyl starch is a modified amylopectin, a highly branched glucose polymer. The molecule is rapidly hydrolyzed by plasma and hepatic amylases.[26] During initial elimination, small molecules (<50,000 daltons) are primarily excreted by the kidney. Some are extravasated from capillaries and phagocytized by the reticuloendothelial system.[27] Elimination kinetics are complex because of the heterogeneity of hetastarch solutions. After infusion into healthy dogs subjected to hemorrhage, 38 percent was present in the plasma and 31.5 percent had been excreted in the urine 24 hours after infusion.[28] When measured between days 7 and 28 after a single infusion of 25 ml/kg, the half-life varied between 7.5 and 8.4 days.[29]

The duration of plasma expansion is approximately 3 to 24 hours.[26] Multiple hetastarch infusions increase serum half-life in humans, but no data regarding similar administration are available in dogs.

Two commercial hetastarch solutions are available: hetastarch (450/0.7) and pentastarch (260/0.7). The numerical values preceding the slash (e.g., 450) indicate the average molecular weight of the colloid; the numerical values listed after the slash (e.g., 0.7) indicate the degree of hydroxylation of the starch molecules. Half-life is dependent upon the degree of hydroxylation and on the complexity of the molecular structure.

TABLE 15-5
Comparison of Common Colloid Solutions

	Plasma	6% Dextran 70	6% Hetastarch	10% Dextran 40	10% Pentastarch	Gelatin
Potential source	In-house; ABB; Cutter; Alpha Therapeutic	Baxter; Abbott; McGaw	DuPont	Abbott; Baxter; McGaw; Pharmacia	McGaw; DuPont	SmithKline Beecham
Range of molecular weight (1000 daltons)	66–69 (albumin); 200–500 (globulin)	15–160	10–2500	10–90	10–2000	5–100
Average molecular weight (1000 daltons)	119	70	450	40	264	35
Colloid oncotic pressure (mmHg)	20–22	60–64	30–32	80–85	40	45–47
Water-retaining capacity (ml/g) [sustained]	13–18	20–25	15–20	20–25	15–25	
Volume expansion (% volume infused) [immediate]	67	75	71	81		70
Volume expansion (% volume infused) [sustained]	9	32		33		19

The osmolality of a colloidal solution suspended in an isotonic crystalloid is about 300 mOsm/kg.
ABB; Animal Blood Bank, Dixon, CA (916) 678-7350
Abbott, Abbott Park, IL (800) 222-6883
Alpha Therapeutic, Los Angeles, CA (213) 225-2221
Baxter Healthcare, Round Lake, IL (800) 933-0303
Cutter (Miles) Pharmaceutical, West Haven, CT (203) 937-2000
DuPont, Wilmington, DE (800) 441-7516
McGaw, Irvine, CA (714) 660-2000
Pharmacia, Piscataway, NJ (732) 457-8000
SmithKline Beecham, Exton, PA

Hetastarch has extremely low toxicity and does not adversely affect cell-mediated immune functions.[29a] In people, it has rarely been associated with allergic reactions. In cats, the LD_{50} of a single acute dose is greater than 4.5 g/kg (75 ml/kg).[29b] Dogs have tolerated doses of 130 to 250 ml/kg and 200 to 1000 ml/kg during a period of 2 to 5 days and 3 to 38 days, respectively.[30] Doses of 200 ml/kg administered to hypoproteinemic dogs over a 5-hour period resulted in no adverse effects.[31] Hetastarch does not interfere with red cell typing and cross-matching procedures, although it may be associated with a doubling of serum amylase concentrations in the absence of pancreatitis.[26]

Experimental data suggest a number of beneficial renal effects of hetastarch administration. During severe hemorrhagic shock, it appears to support renal function.[32] Reversal of oliguric renal failure has been reported after early administration.[33] Doses of 20 ml/kg improved renal dysfunction in hypotensive and normotensive dogs.[34]

Hetastarch can affect some coagulation parameters; it may decrease all components of factor VIII–related complex and should therefore be used with caution when von Willebrand's disease is known or suspected.[35] Otherwise, doses of less than 1 to 1.5 g/kg (16 to 25 ml/kg) probably have few serious deleterious effects on coagulation. Hetastarch affects plasma volume variably, depending in part on the degree of extravascular fluid expansion and initial plasma volume.[36] The average plasma expansion in normovolemic dogs who were administered 25 ml/kg of hetastarch was 137 percent of infused volume.[28] After infusing an average of 50 ml/kg of hetastarch in dogs with hemorrhage, postinfusion plasma values exceeded preinfusion values by more than 200 percent.[37] The duration of plasma expansion after a single dose is between 24 and 48 hours.[27–30]

The recommended initial dose of hetastarch is 10 to 30 ml/kg/day. Animals may benefit from concurrent crystalloid fluid support representing about two thirds of the calculated dose.[36]

DEXTRANS. Dextrans are mixtures of linear polysaccharides produced by the bacteria *Leuconostoc mesenteroides* or lactobacilli on sucrose media. Subsequent acid hydrolysis produces commercially available molecular weight dextrans. Molecular weights above 50,000 daltons are widely distributed in the body and are metabolized by dextrinases at the rate of 70 mg/kg of body weight/day.[38]

Dextran 40 is rapidly filtered by the glomerulus and may be associated with an osmotic diuresis and high urine specific gravity. In states of active tubular reabsorption of sodium and water, such as occurs in dehydration, dextran molecules concentrate in the tubular lumen, increase the filtrate viscosity, and perhaps pre-

cipitate. This may plug the tubule and cause acute renal failure.[26] Dextran 70 and hetastarch have not been implicated as a cause of acute renal failure. Compared with dextran 70, dextran 40 (1) is more hyperoncotic, (2) causes greater initial blood volume expansion, (3) has a shorter duration of action (1.5 to 4 hours), and (4) significantly lowers blood erythrocyte aggregating capacity, viscosity, and microvascular sludging. Dextrans are dosed at 20 ml/kg for the first 24 hours and 10 ml/kg per 24 hours thereafter.

Dextrans produce a dose-related defect of primary hemostasis which is greater than that due to simple dilution alone.[39] Prolongation of activated partial thromboplastin time (APTT) is attributed to a reduction of factor VIII:C activity. Prolonged bleeding time and decreased platelet adhesiveness are attributed to inhibition of the von Willebrand factor–antigen activity. Although it is not expected that even large doses would induce bleeding in normal dogs, dextrans should be used conservatively when von Willebrand's disease or other bleeding tendencies are suspected. This effect on coagulation and platelet function may potentially be therapeutic in thromboembolic diseases.

Additional problems with dextran administration have been reported. Dextrans interfere with red cell typing and cross-matching procedures. Therefore, this must be taken into account if blood transfusion is contemplated. Naturally occurring dextran antibodies exist in the general human population, resulting from exposure to dietary and gastrointestinal tract bacteria-produced dextrans. The incidence of reactions has been rare following reformulation of these products.[26] Allergic reactions have not been reported in animals. Dextran 70 is antigenic, interferes with blood typing and cross-matching due to rouleaux formation, interferes with blood glucose measurement, and must be stored at stable temperatures (25° C) to avoid precipitates.

BLOOD PRODUCTS

PLASMA. Species-matched plasma directly replaces fluid and protein lost to extravascular spaces. Plasma is not as efficient as other colloids for increasing plasma colloid oncotic pressures and plasma volume. When preparing blood components, plasma is separated as blood is centrifuged at a speed to achieve 5000 g for 30 minutes at 1 to 6° C. Plasma is then expressed into a satellite bag and units of plasma (200 to 300 ml) should be frozen for future use. Fresh plasma is made by separating it from whole blood within 3 to 4 hours of collection; it should be used within 24 hours.[40] Approximate initial dose is 10 ml/kg.

ALBUMIN. Albumin comprises about 50 percent of the total plasma protein and affects about 80 percent of the total plasma colloid oncotic pressure. There is approximately 4 to 5 g of albumin/kg in extracellular fluid.[41] Approximately 35 percent of the total is located in the interstitial space.[26, 41] Albumin synthesis is regulated by colloid osmoreceptors in the hepatic endoplasmic reticulum.[42] Synthesis may be inhibited by artificial colloid administration or hyperglobulinemia.[43]

Albumin helps maintain intravascular colloid oncotic pressure and volume. It has a strong negative charge and is an important carrier of certain drugs, hormones, metals, enzymes, chemicals, and toxins (e.g., cations, anions, toxic oxygen radicals, toxic inflammatory substances).[26] Albumin is administered in humans to maintain plasma proteins without affecting clotting function.[44] The plasma half-life is 16 hours and the body half-life (in healthy people) is about 20 days.[41] Usage in veterinary medicine is currently restricted by availability, lack of clinical trials, and the potential for antigenic reactions following repeated administrations. Formulation of a 3 percent albumin preparation can be made by adding 12 ml of 25 percent human albumin to 488 ml of lactated Ringer's solution; it is administered at 20 ml/kg intravenously.[45]

WHOLE BLOOD. Hemoglobin is a major factor in determining blood oxygen content. Thus, when hemoglobin concentration decreases, oxygen content decreases and oxygen delivery may become inadequate. Depending upon other factors, including cardiac output and PaO_2, oxygen delivery may become deficient when the hemoglobin is reduced to less than 5 to 10 g/dl (packed cell volume below 15 to 30 percent). Therapeutically, hemoglobin concentration must be maintained in high-normal ranges when blood oxygenation and cardiac output are compromised as in septic shock or multiple organ dysfunction syndrome.

In dogs, naturally occurring isoantibodies are uncommon and only weakly antigenic.[46] With first-time transfusions, reactions are reported to be uncommon when cross-matching is not performed. When they do occur, their severity is often minimal. However, dogs that have had a transfusion greater than 5 days previously should be cross-matched. Donor blood should be negative for dog erythrocyte antigen (DEA) 1.1. The importance of DEA 1.2 and DEA 7 in transfusion reactions is controversial because they are weakly antigenic.[47]

In cats, naturally occurring isoantibodies occur and it is advisable that cats should be cross-matched prior to transfusion. Type A cats have low titers of naturally occurring anti-B antibodies, but Type B cats have high titers of strong, naturally occurring anti-A antibodies. Mean red blood cell survival times in matched transfusions were 38 days in one report.[48] Transfusion of Type B blood into Type A cats was associated with a mean red blood cell survival time of 2 days and only minor transfusion reactions, whereas transfusion of Type A

blood into Type B cats was associated with a mean red blood cell survival time of 1 hour and severe transfusion reactions.[49] A compatible major cross-match of the blood donor with the untyped recipient identifies a safe transfusion and a blood Type A recipient. An incompatible major cross-match of Type A and untyped recipient identified an unsafe transfusion and a blood Type B recipient.[50]

Blood typing of donor cats is necessary. Cats most likely to be Type A are the domestic shorthair and longhair "mongrel" cats. Type B cats are most common in Scottish Fold, Birman, Himalayan, Abyssinian, Somali, Persian, Devon Rex, and British shorthair breeds.[51, 52]

The volume of blood to be transfused depends upon (1) the degree of anemia, (2) the time over which it occurred, and (3) the extent of ongoing hemorrhage or hemolysis. When 2.2 ml/kg of whole blood is administered to anemic cats, the packed cell volume (PCV) increases approximately 1 percent.[53] Alternatively, a general formula may be used to calculate the required transfusion volume of whole blood required to increase recipient PCV to a desired level:

$$\text{Volume (whole blood)} = \text{body wt (kg)} \times (66 \text{ for cats, } 88 \text{ for dogs}) \times \frac{\text{Desired PCV} - \text{Recipient PCV}}{\text{PCV of transfused blood}}$$

where species blood volume is approximately equal to 66 ml/kg in cats and 88 mg/ml in dogs.[54] A general rule of thumb to guide the amount of blood to be administered is: dogs receive 10 to 40 ml/kg and cats receive 5 to 20 ml/kg for small to large transfusions, respectively. Whole blood and plasma is administered over about 2 to 4 hours to minimize clinical manifestations of volume overload or foreign protein histamine-mediated reactions. Immunologic transfusion reactions may be clinically manifested by restlessness, acute collapse, hypotension, dyspnea, wheezing, urticaria, hemoglobinemia, hemoglobinuria, or fever. If any of these signs develop, the transfusion should be stopped immediately.[55]

RED BLOOD CELL SUBSTITUTES. The quest for oxygen-carrying red blood cell substitutes intensified when human acquired immunodeficiency syndrome (AIDS) increased the risk for blood-borne transmission. One blood substitute, Oxyglobin® (Biopure Corp., Cambridge, MA), is a bovine-derived, ultrapure, polymerized hemoglobin solution (hemoglobin concentration, 13 g/dl) that has recently received veterinary FDA approval.[56] Recommended dosage in dogs is a one time dose of 30 ml/kg administered IV at a rate of up to 10 ml/kg/hr. The major veterinary indication for red blood cell substitutes is acute, reversible anemia.

CARDIAC SUPPORT

Cardiotonics may be required in some cases to maintain cardiac contractile function. A constant rate infusion of dobutamine or dopamine is usually selected (see later; also, see chapter 12).

INTEGRATED MONITORING OF CARDIOPULMONARY FUNCTION

The purpose of fluid therapy in shock is to restore effective circulating volume to "supranormal" levels (chapter 14). Determination of efficacy involves a number of clinical observations and measured assessments. These include mucous membrane color and capillary refill time; appendage temperature; urine output; heart rate; and femoral arterial pulse quality. In animals that respond well to fluid therapy, this level of monitoring is usually sufficient. A number of patients, however, fail to respond to fluid therapy alone and do not attain acceptable cardiovascular improvement. Therapy in these cases is modified to include additional fluids and sympathomimetic drugs. Ideally, appropriate management decisions are guided by basic cardiovascular monitoring in addition to clinical signs and assessments.

CENTRAL VENOUS PRESSURE

The central venous pressure (CVP) is affected by venous blood volume (venous return), venomotor tone, ventricular compliance, and cardiac output. It is indirectly associated with right ventricular preload (end-diastolic filling volume) when diastolic function is normal and elevated values suggest high right ventricular filling volume. Measurements of CVP should be interpreted with reference to patient history, physical examination and other parameters of cardiovascular function. A CVP of less than 5 cm H_2O suggests that additional fluids or increased administration rates are necessary. Alternatively, a CVP greater than 10 cm H_2O suggests that the rate of fluid therapy administration is sufficient or excessive, depending upon clinical conditions and signs.

ARTERIAL BLOOD PRESSURE

Monitoring arterial blood pressure (ABP) may be important, especially when treating conditions associated with impaired myocardial contractility, hypotension, or large fluxes in vascular volume. Arterial blood

TABLE 15–6
Hemodynamic Parameters Used for Patient Monitoring

Measured Parameters

Arterial blood pressure
Central venous pressure
Cardiac output
Arterial blood gases
Mixed venous blood gases
Pulmonary artery occlusion pressure (wedge pressure)
Hemoglobin (packed cell volume)

Calculated Variables

Variable	*Formula*	*Units*
Cardiac index	CI = Cardiac output/BSA	L/min · m^2
Systemic vascular resistance index	SVRI = 79.92* (MAP − CVP)/CI	dyne · sec/cm^5 · m^2
Pulmonary vascular resistance index	PVRI − 79.92* (MPAP − WP)/CI	dyne · sec/cm^5 · m^2
Mean transit time	Direct measurement	sec
Central blood volume	CBV = MTT × CI × 16.7	ml/m^2
Stroke index	SI = CI/HR	ml/m^2
Left ventricular stroke work	LVSW = SI × MAP × 0.0144*	g · m/m^2
Right ventricular stroke work	RVSW = SI × MPAP × 0.0144*	g · m/m^2
Left cardiac work	LCW = CI × MAP × 0.0144*	kg · m/m^2
Right cardiac work	RCW = CI × MAP × 0.0144*	kg · m/m^2
Oxygen delivery	DO_2 = CI × CaO_2 × 10	ml/min^2 · m^2
Oxygen consumption	VO_2 = CI × $C(a-v)O_2$ × 10	ml/min · m^2

*0.0144 and 79.92 are conversion factors.
BSA, body surface area; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; WP, pulmonary wedge pressure; MTT, mean transit time; HR, heart rate; CaO_2, arterial O_2 content; $C(a - v)O_2$, arteriovenous O_2 difference.

pressure is the product of cardiac output times systemic vascular resistance (chapter 35). Mean pressure should be maintained at greater than 60 mmHg and systolic pressure at greater than 80 mmHg. Normal blood pressure does not insure the presence of acceptable cardiovascular function—it assures only that one component of it may be adequate. Moreover, although arterial blood pressure may be within the normal range, it may not indicate appropriate cardiac output and tissue perfusion since persistent vasoconstriction may normalize pressure measurements. If arterial blood pressure is low after fluid therapy while CVP is high, sympathomimetics may be indicated.

CARDIOVASCULAR CATHETERIZATION FOR HEMODYNAMIC MONITORING

Placement of a balloon-tipped, thermodilution cardiac output catheter allows the measurement and calculation of various hemodynamic parameters (Table 15–6; see also Figure 14–1); these provide a comprehensive overview of cardiovascular status (Table 15–7).[57] As discussed in chapter 14, such evaluations may be especially beneficial in critically ill or unstable patients, or when CVP and arterial blood pressure are normal but clinical parameters of tissue perfusion and arterial pulse quality are still suboptimal.

The interrelationships of hemodynamic and cardiovascular parameters are illustrated in Figure 15–1. Pulmonary occlusion pressure (i.e., pulmonary capillary wedge pressure, PCWP) is a measurement of left-sided heart preload. Acute left-sided heart failure or fluid overload can cause a PCWP of greater than 15 mmHg, and monitoring this parameter may be useful during aggressive vasodilator therapy, especially when sodium nitroprusside is administered. Cardiac output can be evaluated by thermodilution and used as an index of

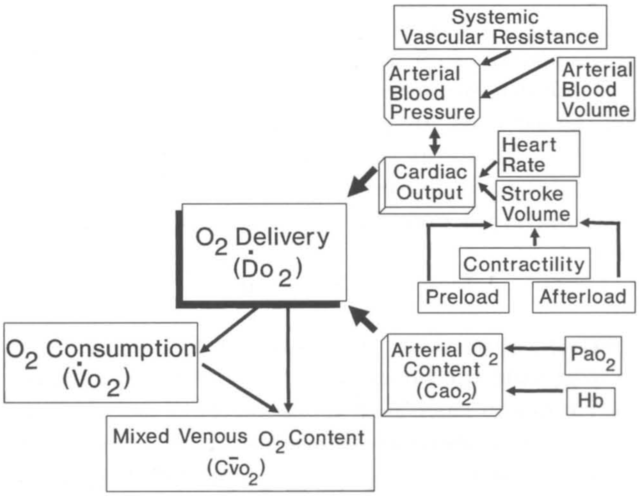


FIGURE 15–1

Important hemodynamic relationships in management of shock. Hb, hemoglobin concentration; PaO_2, partial pressure of oxygen in arterial blood.

TABLE 15–7
Normal and Minimally Acceptable Cardiopulmonary Values to Guide Therapy in Critically Ill Patients

Parameter	Normal Value	Minimally Acceptable Value	Optimal
Arterial blood pressure (mmHg) (mean)	80–120	60–80	80–120
Central venous pressure (cm H_2O)	0–10	>6	8–10
Cardiac output (L/m^2/min)	3.5–5.5	>4	>5
PaO_2 (mmHg)	80–110	>60	>80
SaO_2 (mmHg)	98–99	>90	>95
$PaCO_2$ (mmHg)	35–45	<60	35–45
PvO_2 (mmHg)	40–50	>30	>40
Pulmonary artery occlusion pressure (mmHg)	8–12	>6	10–14
Systemic vascular resistance (dynes · sec · cm^2)	16,000–24,000	>500; <2500	500–1500
Pulmonary vascular resistance (dynes · sec · cm^5)	150–200	—	—
Hemoglobin (g/dl)	13–16	>7–8	>9–10
Systemic oxygen delivery (L/m^2/min)	600–900	>600	>800
Oxygen consumption (L/m^2/min)	150–200	>100	>150
Oxygen extraction (%)	20–30	<35	<25
Venous admixture (%)	<10%	As low as possible	As low as possible

the heart's ability to accept and eject blood adequately. A low cardiac output can be caused by reduced preload (e.g., severe volume contraction from dehydration, blood loss, overdiuresis, conditions of ventricular underfilling such as cardiac tamponade) or poor contractility.

OXYGEN DELIVERY AND CONSUMPTION. As described in chapter 14, oxygen delivery and consumption must be optimized to effect a successful outcome. Common causes of decreased oxygen delivery include reduced cardiac output or low arterial oxygen content. The latter is often due to anemia or hypoxemia. Low oxygen consumption may be attributed to insufficient oxygen delivery, shunting of blood past metabolically active tissue beds, or intrinsically impaired metabolic function. Attention is focused on methods to assure optimal oxygen delivery, provide vascular volume support and avoid excessive vasoconstriction or vasodilation.

VENOUS ADMIXTURE. This expresses the lung's ability to oxygenate the blood. It is a better index of pulmonary function than PaO_2 alone or the alveolar-arterial PO_2 gradient and may be elevated in the respiratory distress syndrome or septic multiorgan dysfunction syndrome. Management options include oxygen administration to optimize ventilation/perfusion or positive pressure ventilation to reopen collapsed small airways and alveoli.

DRUG THERAPIES

SYMPATHOMIMETIC AGENTS

Certain drugs (Table 15–8) may be indicated for cardiovascular support when fluid therapy alone has failed to restore acceptable tissue perfusion, pulse quality, arterial blood pressure, and cardiac output, or to reduce elevated central venous or pulmonary artery occlusion pressures.[58–60] Inotropes may be required to maintain or increase cardiac output. Pressor agents may be needed to increase arterial blood pressure, but excessive vasoconstriction may impair tissue perfusion. Vasodilators may be useful to improve cardiac output and tissue perfusion, but may cause hypotension and a reduction in PaO_2. More aggressive oxygenation and ventilation support may be indicated if significant hypoxemia develops.

Untoward reactions to sympathomimetics relate to their agonist effects. These include sinus tachycardia, extrasystoles, and increased myocardial oxygen utilization with β_1-agonists; systemic hypertension with α_1-agonists; and hypotension occurring with β_2-agonists, α_1-blockers, or direct-acting vasodilators. Dopamine and dobutamine are the most commonly used inotropic agents in shock therapy.

DOPAMINE. This drug exhibits both direct and indirect cardiovascular effects, half of which is attributed to norepinephrine release from sympathetic nerve

TABLE 15-8
Cardiotonic and Vasoactive Drugs Used in Septic Shock

Agent	Receptor Activity β	Receptor Activity α	Dosage	Indication
Dobutamine	+ + +	+	2.5–15 μg/kg/min	Low Q, high SVR
Dopamine	+ + +	+ +	3–10 μg/kg/min	Low Q, SVR, ABP
Epinephrine	+ + +	+ + +	0.1–1 μg/kg/min	When patient nonresponsive to dopamine
Norepinephrine	+	+ + +	0.1–1 μg/kg/min	Low SVR, ABP
Phenylephrine	—	+ + +	25–100 μg/kg/min	Low SVR, ABP
Ephedrine	+	+	0.05–0.2 mg/kg	Same as dopamine
Nitroprusside	Direct vasodilation		1–3 μg/kg/min	High SVR
Hydralazine	Direct vasodilation		0.2–0.5 mg/kg	High SVR

Q, cardiac output; SVR, systemic vascular resistance; ABP, arterial blood pressure.

endings. Effects are dose related.[61–63] The duration of beneficial effects is limited due to depletion of presynaptic dopaminergic reserves, receptor sequestration, or down regulation.[62] At low dosages (1 to 2 μg/kg/min), β_2-agonist and dopaminergic actions dominate, which enhance blood flow to renal and splanchnic beds (except liver). Moderate doses (3 to 5 μg/kg/min accentuate cardiac inotropy, and at higher doses (5 to 10 μg/kg/min), vasoconstriction predominates.

Dopamine is preferred over dobutamine if an increase in arterial blood pressure is the desired endpoint. Greater pressor activity (and arrhythmogenicity) manifests as the dose increases. Higher doses may cause excessive vasoconstriction, and further dose increases provide no improvement in cardiac output or oxygen delivery. Dopamine constricts capacitance veins and may increase central venous and pulmonary occlusion pressures.[64] Dopamine also decreases aldosterone secretion.[65]

DOBUTAMINE. A direct-acting synthetic catecholamine, dobutamine increases cardiac output, oxygen delivery, and oxygen consumption more reliably than dopamine, primarily because dobutamine does not cause vasoconstriction. Dobutamine has potent β_1-(cardiac stimulatory) and modest β_2-(vasodilatory) properties, with lesser α_1-agonist activity. Its major metabolite, 3-*O*-methyldobutamine, is an $\alpha_{1,2}$-inhibitor. Dobutamine administration is usually associated with a decrease in systemic vascular resistance, central venous pressure, and pulmonary occlusion pressure but can increase myocardial oxygen utilization. The ideal candidate for dobutamine therapy is an animal with severely depressed myocardial contractility, with elevated filling pressures but without hypotension (mean arterial blood pressure >80 mmHg). In heart failure patients, dobutamine reduces systemic vascular resistance and increases cardiac output while arterial blood pressure remains relatively constant.[66] Dosage is 2.5 to 15 μg/kg/min. In cats, doses greater than 5 μ/kg/min may induce seizures.[67]

OTHER DRUGS TO SUPPORT CARDIAC OUTPUT AND BLOOD PRESSURE

Epinephrine has potent $\beta_{1,2}$- and $\alpha_{1,2}$-agonist activities that are dose related. Lower dosages increase cardiac output with minimal changes in systemic vascular resistance. Higher dosages increase systemic vascular resistance and arterial blood pressure with no further improvement in cardiac output. Epinephrine is most commonly used in cardiac arrest (chapter 21) and only occasionally in shock states unresponsive to dobutamine or dopamine. *Ephedrine* is an indirect-acting sympathomimetic drug that causes norepinephrine release from sympathetic nerve endings. Although not as potent or effective as dopamine and dobutamine, it has a longer duration of action. *Norepinephrine* and *phenylephrine* are occasionally administered if arterial blood pressure cannot be stabilized with any of the other agents. These potent vasopressors should be used with caution because intense peripheral vasoconstriction may impair organ perfusion.

VASODILATORS

Hydralazine and *nitroprusside.* These drugs are occasionally used to treat acute, severe cardiogenic pulmonary edema (chapters 12, 13) and are uncommonly administered for shock therapy. Hydralazine is an arteriolar vasodilator. When administered orally, it exerts significant arteriolar dilation and afterload reduction by 1 hour postadministration. Nitroprusside is a potent mixed arteriolar and venous vasodilator administered by constant rate infusion. It acts immediately, and

blood pressure must be carefully monitored to avoid hypotension.

ANTIMICROBIAL AGENTS

In shock, antibiotics should be administered by the parenteral route because of reduced gastrointestinal drug absorption. Because pathogen type and the spectrum of antibiotic sensitivity cannot be known initially, a choice of broad-spectrum antimicrobial agent(s) should be favored (Table 15–9). Selection should also incorporate information about pharmacokinetics, antimicrobial characteristics, and patient status. Reported bacteremias are gram-negative 30 to 70 percent of the time, gram-positive in 25 to 50 percent, anaerobic in 10 to 30 percent, and of mixed infection in approximately 10 to 50 percent.[68–70a]

AMINOGLYCOSIDES. Gentamicin, amikacin, netilmicin, and tobramycin are effective against most gram-negative organisms and *Staphylococcus aureus;* they are not very effective against *Streptococcus* spp and anaerobes.[71–74]

FLUOROQUINOLONES. Enrofloxacin (Baytril), norfloxacin, and ciprofloxacin exhibit a spectrum of activity similar to that of aminoglycosides. However, resistance is not plasmid-mediated, and therefore quinolone antibiotics may be effective when resistance has developed to aminoglycosides.[72] Thus they should not be used indiscriminately when equally efficacious agents are available.

BETA-LACTAMS. The usefulness of these popularly administered antibiotics is related to their safety, efficacy, and cost.

PENICILLINS. Penicillin G, ampicillin, and amoxicillin are generally effective against gram-positive (*Streptococcus* sp and some *Staphylococcus* spp) and all anaerobic bacteria except beta-lactamase–producing strains of *Bacteroides fragilis* and *Actinomyces hordeovulnaris.* They are not effective against gram-negative organisms. The beta-lactamase resistant penicillins (methicillin, nafcillin, oxacillin, cloxacillin) are generally effective against *Staphylococcus* spp but, in general, are not effective against anaerobes and gram-negative bacteria.[73–75] The extended-spectrum carboxypenicillins (ticarcillin and carbenicillin), and the extended-spectrum ureidopenicillins (azlocillin, piperacillin, mezlocillin) are broad-spectrum antibiotics with expanded activity against

TABLE 15–9
Antimicrobials and Spectrums of Activity

Agent	Gram-Negative Spectrum	Gram-Positive Spectrum (*Staph* sp;	*Strep* sp)	Anaerobic Spectrum
Penicillins: penicillin G ampicillin amoxicillin	no	often	yes	Yes (except some *B. fragilis* and actinomyces)
Beta-lactamase–resistant penicillins: oxacillin methicillin nafcillin cloxacillin	no	yes	yes	no
Extended-spectrum penicillins: carbenicillin ticarcillin	yes	yes	yes	yes
Extended-spectrum ureidopenicillins: azlocillin piperacillin mezlocillin				
Cephalosporins:				
1st generation	some	yes	yes	no
2nd generation	yes (except *Pseudomonas*)	yes	yes	variable
3rd generation	yes	yes	yes	yes
Imipenem/cilastatin	yes	yes	yes	yes
Aminoglycosides	yes	yes	no	no
Fluoroquinolones	yes	yes	no	no
Aztreonam	yes	no	no	no
Metronidazole	no	no	no	yes
Clindamycin	no	yes	yes	yes

Staphylococcus sp and gram-negative and anaerobic bacteria.[71, 72, 74, 76] Broad-spectrum effectiveness is enhanced when they are combined with beta-lactam enzyme inhibitors such as sulbactam or clavulinic acid.

CEPHALOSPORINS. First-generation cephalosporins (cephalothin, cefazolin, cephalexin, cephapirin, cephadrine, cefadroxil) are effective against gram-positive bacteria. However, they have intermediate effectiveness against gram-negative bacteria and are generally ineffective against anaerobes (especially *B. fragilis* and other *Bacteroides* spp).[71, 72, 77] Second-generation cephalosporins (cefoxitin, cefamandole, cefaclor, cefuroxime, cefonicid, ceforanide, cephotetan, cefmetazole) are effective against some anaerobes (including *B. fragilis* and other *Bacteroides* spp) and gram-negative organisms (except *Pseudomonas* spp).[71, 72, 74, 77] Third-generation cephalosporins (cefotaxime, moxalactam, cefoperazone, ceftizoxime, ceftriaxone, ceftazidime, cefixime) have a gram-positive, gram-negative, and anaerobic spectrum; are highly beta-lactamase–resistant;[71, 77] and probably are sufficiently effective and broad-spectrum to be used as the sole antibiotic.

CARBAPENEMS. Beta-lactamase is the most common cause of resistance to extended-spectrum penicillins. Third-generation cephalosporins and these newer-generation agents are resistant to β-lactamase–secreting organisms. Imipenem/cilastatin is resistant to Type I beta-lactamase and provides good, broad-spectrum coverage.[78]

MONOBACTAMS. Aztreonam is effective against most gram-negative bacteria *(Escherichia coli, Klebsiella, Proteus, Enterobacter);* however, it is not reliable for gram-positive and anaerobic bacteria.[74]

MACROLIDES. Clindamycin has a good spectrum of activity against *Streptococcus* spp, *Staphylococcus* spp, and many anaerobes (especially *Bacteroides* spp) but not gram-negative bacteria.[73, 76] When used parenterally, it should be infused over a 30-minute period to avoid hypotension.

OTHER AGENTS. Sepsis can also be caused by rickettsial, protozoan, chlamydial, and viral infections, in which case the aforementioned antimicrobial agents may not be effective. Metronidazole (Flagyl) is effective against protozoa and obligate anaerobic bacteria (especially *Bacteroides* spp). It is not effective against facultative anaerobes or obligate aerobes.[71, 73] Rickettsia are usually susceptible to tetracycline, doxycycline, chloramphenicol, and imidocarb dipropionate. Chlamydia are usually susceptible to tetracycline, doxycycline, and chloramphenicol. Protozoa are usually susceptible to metronidazole, quinacrine hydrochloride, imidocarb dipropionate, amprolium, pyrimethamine, and clindamycin.[79]

GLUCOCORTICOSTEROIDS

Corticosteroids have been advocated in shock for various reasons: organelle and cell membrane stabilization, improved cellular metabolism and gluconeogenesis, improved microcirculation, decreased production of endogenous toxins (e.g., myocardial depressant factor), decreased leukocyte activation and degranulation, and minimized reticuloendothelial depression and histologic organ damage. Agents generally recommended for hypovolemic and septic shock include hydrocortisone (100 to 300 mg/kg); prednisolone and methylprednisolone (10 to 30 mg/kg); and dexamethasone (4 to 6 mg/kg).[80–82]

Studies evaluating the efficacy of large-dose corticosteroids in the treatment of septic shock have been conducted in humans[83–86, 88, 89] and animals.[87] Improved survival was reported by some investigators;[87–89] others recorded more frequent reversal of shock in steroid-treated patients compared with controls, but without improved survival rates.[83] No improvement in survival or reversal of the shock state was observed using methylprednisolone, 30 mg/kg plus 5 mg/kg/hr for 9 hours[85] or 30 mg/kg repeated three times at 6-hour intervals for 24 hours.[85, 86] Moreover, no significant differences were found in the incidence of secondary infections between steroid-treated versus untreated groups, although steroid-treated patients had higher mortality when secondary infections were present compared with the patients not given steroids.[84, 87] A beneficial effect on survival was achieved with modest doses of hydrocortisone in septic shock patients.[89a]

Glucocorticoids are generally beneficial for treatment of shock associated with adrenal insufficiency and hypothyroidism. They are not indicated for cardiogenic shock.

ANTIPROSTAGLANDINS

Prostaglandins that are released into the systemic circulation during shock cause marked hemodynamic changes. These include decreased cardiac output, systemic hypotension, pulmonary hypertension, and increased vascular permeability. Experimental treatment with antiprostaglandins ameliorates these cardiovascular changes and improves survival but generally does not affect the leukopenia, thrombocytopenia, acidosis, or coagulopathies that develop during septic shock. Adverse effects of antiprostaglandins include gastrointestinal tract hemorrhage and ulceration, which are augmented by coadministration of corticosteroids. Renal afferent vasoconstriction has been reported when

ibuprofen was administered during septic shock in dogs.[90] The clinical usefulness of antiprostaglandins awaits further investigation.

GLUCOSE

If the blood glucose concentration is very low, a bolus of glucose (0.25 g/kg IV) should be administered. Adequate blood glucose concentration is then maintained by an infusion of a 2.5 to 10 percent glucose solution, titrated to the desired effect.

SODIUM BICARBONATE

Sodium bicarbonate should be administered if metabolic acidosis becomes severe during shock. If the base or bicarbonate deficit is known, the dose of bicarbonate can be calculated as:

$$\text{Sodium bicarbonate dose} = \text{Base deficit} \times [0.3 \times \text{body weight (kg)}]$$

If the magnitude of metabolic acidosis cannot be measured but is estimated on the basis of clinical signs as moderate to severe, then sodium bicarbonate, 3 to 5 mEq/kg, may be administrated slowly over 20 minutes.

EFFECTS OF SHOCK ON SPECIFIC ORGANS

THE HEART

HEART FAILURE. Impaired myocardial contractility is an early consequence of septic shock. The heart may become unable to compensate for hypotension resulting from arterial vasodilation or hypovolemia. Coronary perfusion may be compromised, further reducing cardiac function. The left ventricular ejection fraction becomes depressed, resulting in further hypotension, inadequate tissue oxygen delivery, and multiple organ failure. Volume resuscitation with sympathomimetic cardiovascular support is indicated.[91]

THE KIDNEYS

ACUTE RENAL FAILURE. Urine output is an indirect indicator of renal blood flow. Anuria suggests inadequate renal (and visceral) perfusion that may precipitate acute organ failure if excessive or prolonged. Oliguria is a cardinal manifestation of shock. A urinary catheter should be placed to verify and quantify urine output.

Fluid administration is the mainstay of renal perfusion and for inducing diuresis. If restoration of an effective circulating volume does not generate an acceptable urine flow, diuretics should be administered. Furosemide, 5 mg/kg, intravenously, is a potent loop diuretic that promotes mild renal (and visceral) vasodilation. If urine flow is not detected within 10 minutes, the dose may be doubled or a different diuretic administered. Mannitol, 0.5 g/kg, intravenously administered over 10 to 20 minutes, osmotically increases blood volume and renal perfusion and subsequently acts as an osmotic diuretic. If urine flow is not detected within 10 minutes following the end of the mannitol infusion, another agent should be administered. Dopamine, 1 to 3 μg/kg/min, intravenously, causes renal (and visceral) vasodilation via dopaminergic-receptor stimulation. If each drug individually fails to induce an acceptable urine output, simultaneous administration of all agents may be attempted.

THE GASTROINTESTINAL TRACT

HEMORRHAGE AND MUCOSAL SLOUGHING. Gastrointestinal tract hemorrhage, mucosal ulceration, and sloughing are common consequences of septic shock. Mechanisms may be related to tissue hypoxia and diminished organ perfusion, oxygen radical–induced cell membrane lipid peroxidation, diffusion of luminal hydrogen ions into mucosal cells, deterioration of the effectiveness of the mucous barrier, destructive action of bile acids and pancreatic proteases, or some combination of these causes.[92, 93]

The mainstay of gastrointestinal tract protection involves (1) restoration of an effective circulating blood volume, and (2) re-establishment of adequate visceral perfusion and oxygenation. Drugs such as cimetidine and ranitidine, which block histamine (H_2) receptors, decrease gastric acid secretion, as do some anticholinergic agents such as glycopyrrolate. Sucralfate acts to coat and protect existing epithelial erosions. Misoprostol, a prostaglandin E_2 analogue, and superoxide dismutase and catalase, oxygen radical scavengers, have been reported to diminish gastric injury in a septic shock. Methylprednisolone, however, was more effective in this regard than was a combination treatment of misoprostol, superoxide dismutase, and catalase.[92] Clinical efficacy awaits additional trials.

THE LUNGS

RESPIRATORY FAILURE. Adult respiratory distress syndrome (ARDS) is a diffuse, infiltrative pulmonary parenchymal disease that is a common sequela to trauma, shock, sepsis, and a variety of pulmonary insults. It is also receiving more attention in veterinary medicine. This syndrome is caused by increased pulmonary capil-

lary permeability resulting from a series of complex systemic inflammatory interactions. This diffuse infiltrative process decreases lung compliance, increases the work of ventilation, and ultimately causes small airway and alveolar collapse, increased venous admixture, and refractory hypoxemia.[94]

Oxygen therapy may be initially palliative. As the condition worsens, positive pressure ventilation becomes necessary to re-expand small airways and alveoli. Aggressive ventilatory settings are often necessary due to the severely reduced compliance of these lungs.

THE BLOOD

COAGULOPATHIES. Activation of the coagulation and platelet aggregation cascades is an early consequence of the systemic inflammatory response syndrome and multiple organ dysfunction syndrome. Acute disseminated intravascular coagulation (DIC) is often present. Endogenous fibrinolysis leads to a rise in plasma fibrin degradation products. Small vessel thrombosis may cause microangiopathic red blood cell fragmentation (schistocytes) and intravascular and extravascular hemolysis. Hypocoagulopathy may develop secondary to depletion of coagulation precursors or accumulation of fibrin degradation products and is associated with multifocal hemorrhage, prolonged coagulation times, impaired clot formation, depletion of antithrombin III (AT III), thrombocytopenia, and hypofibrinogenemia.

Management of DIC involves several key steps: (1) Treatment of the underlying disease process is the single most important objective; (2) Crystalloid fluid is administered to maximize microcirculation (i.e., induce modest hemodilution); (3) The hypercoagulative state is treated to diminish thrombogenesis (e.g., heparin, 100 μ/kg subcutaneously every 6 hours) with the objective of impairing further coagulation; platelet aggregation can be inhibited by oral aspirin or dextran infusion; (4) Underlying prothrombotic factors (i.e., stasis, sepsis, dehydration, AT III deficiency) are modified; and (5) secondary complications are prevented.[95]

METABOLIC INJURY

NUTRITIONAL SUPPORT. Early nutritional support (within 24 to 48 hours of hospitalization) represents an important aspect of critical care management.[96] Enteral feeding is preferable for several reasons. It preserves gut mucosal mass, gut impermeability, and mucosal immunity; it reduces infectious complications and release of inflammatory cytokines associated with critical illness; and it improves survival compared with intravenous feeding.

Many animals can be successfully supported by feeding through a nasoesophageal or percutaneous placed gastrostomy (PEG) tube. Some critically ill patients develop ileus that may limit the efficacy of feeding via the stomach. A jejunostomy tube should be considered if the stomach is not emptying appropriately, or if vomiting is a problem. Enteral feeding should provide nutrition for the gut itself and potentially satisfy patient nutritional requirements.

If the enteral feeding is not possible, intravenous feeding is recommended. However, this route is nutritionally inferior to enteral feeding and should not be used as the primary source of nutrition when the gut is working.

TOXIC OXYGEN RADICALS. Toxic oxygen radicals may result from multiple mechanisms, including mitochondrial electron bleed, eicosanoid metabolism, xanthine oxidase action on hypoxanthine, and neutrophilic activation. These oxyradicals may cause tissue injury through (1) protein denaturation and fragmentation, altering both structure, function, and susceptibility to proteolysis; (2) oxidation of polyunsaturated fatty acids, making them more susceptible to hydrolysis by phospholipase A_2; (3) DNA strand breakage; and (4) NAD^+ and ATP depletion.[97]

Antioxidant therapy may have a clinical role in septic multiple organ dysfunction syndrome. Although superoxide dismutase, catalase, glutathione peroxidase, allopurinol, alpha-tocopherol, "lazaroids," corticosteroids, and other agents are being studied, their benefit in shock is speculative at this time.

REFERENCES

1. Deitch EA. Overview of multiple organ failure. *In* Prough DS, Traystman RJ (eds). Critical Care: State of the Art. Society of Critical Care Medicine, Anaheim, CA, 1993, p 131
2. Weil MH. Current understanding of mechanisms and treatment of circulatory shock caused by bacterial infections. Ann Clin Res 9:181, 1977
3. Goldberg RJ, Gore JM, Alpert JS, et al. Cardiogenic shock after acute myocardial infarction: Incidence and mortality from a community-wide perspective, 1975 to 1988. N Engl J Med 325:1117, 1991
4. Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988
5. Califf RM, Bengtson JR. Cardiogenic shock. N Engl J Med 330:1724, 1994
6. Weil MH, von Planta M, Rackow EC. Acute circulatory failure (shock). *In* Braunwald E (ed). Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB Saunders, 1992, p 569
7. Shuster DP, Lefrak SS. Shock. *In* Civetta JM, Taylor RW, Kirby RR (eds). Critical Care. Philadelphia, JB Lippincott, 1988, p 891
8. Hardie EM, Rawlings CA. Septic shock. Part I. Pathophysiology. Compend Con Educ Pract Vet 5:36, 1983
9. Goodwin J-K, Schaer M. Septic shock. Vet Clin North Am 19:1239, 1989

10. Tracey KJ, Lowry SF. The role of cytokine mediators in septic shock. Adv Surg 23:2, 1990
11. Vincent JL, Weil MH, Puri V, et al. Circulatory shock associated with purulent peritonitis. Am J Surg 142:262, 1981
12. Weil MH, Shubin H. The "VIP" approach to the bedside management of shock. J Am Med Assoc 207:337, 1969
13. Shoemaker WC, Montgomery ES, Kaplan E, et al. Physiologic patterns in surviving and nonsurviving shock patients. Arch Surg 106:630, 1973
14. Shoemaker WC, Bland RD, Appel PL. Therapy of critically ill postoperative patients based on outcome prediction and prospective clinical trials. Surg Clin North Am 65:811, 1985
15. Kumar A, Falke KJ, Geffin B, et al. Continuous positive-pressure ventilation in acute respiratory failure. N Engl J Med 283:1430, 1970
16. Walser M, Selfin DW, Grollman A. Measurement of extracellular fluid with radiosulfate. J Clin Invest 31:669, 1952
17. Lamke LO, Liljedahl SO. Plasma volume changes after infusion of various plasma expanders. Resuscitation 5:93, 1976
18. Hauser CJ, Shoemaker WC, Turpin I, et al. Oxygen transport responses to colloid and crystalloid in critically ill surgical patients. Surg Gynecol Obstet 150:811, 1980
19. Nakayama SI, Sibley L, Gunther RA, et al. Small-volume resuscitation with hypertonic saline (2400 mOsm/liter) during hemorrhagic shock. Circ Shock 13:149, 1984
20. Kramer GC, Perron PR, Lindsey DC, et al. Small volume resuscitation with hypertonic saline dextran solution. Surgery 100:239, 1986
21. Velasco IT, Rocha e Silva M, Oliveira MA, et al. Hypertonic and hyperoncotic resuscitation from severe hemorrhagic shock in dogs: A comparative study. Crit Care Med 17:261, 1989
22. Layon J, Duncan D, Gallagher TJ, et al. Hypertonic saline as a resuscitation solution in hemorrhagic shock: Effects on extravascular lung water and cardiopulmonary function. Anesth Analg 66:154, 1987
23. Zoran DL, Jergens AE, Riedesel DH, et al. Evaluation of hemostatic analytes after use of hypertonic saline solution combined with colloids for resuscitation of dogs with hypovolemia. Am J Vet Res 53:1791, 1992
24. Maningas PA, De Guzman LR, Tillman FJ, et al. Small volume infusion of 7.5% NaCl in 6% dextran 70 for the treatment of severe hemorrhagic shock in swine. Ann Emerg Med 15:1131, 1986
25. Linko K, Makelainen A. Cardiorespiratory function after replacement of blood loss with hydroxyethyl starch 120, dextran 70, and Ringer's acetate in pigs. Crit Care Med 17:1031, 1989
26. Falk JL, et al. Colloid and crystalloid fluid resuscitation. *In* Shoemaker WC, Thompson WL, Holbrook PR (eds). Textbook of Critical Care. 2nd ed. Philadelphia, WB Saunders, 1989, p 1060
27. Mishler JM. Synthetic plasma volume expanders: Their pharmacology, safety and clinical efficacy. Clin Haematol 13:75, 1984
28. Thompson WL, Fukushima T, Rutherford RB, et al. Intravascular persistence, tissue storage, and excretion of hydroxyethyl starch. Surg Gynecol Obstet 131:965, 1970
29. Yacobi A, Gibson TP, McEntegart CM, et al. Pharmacokinetics of high molecular weight hydroxyethyl starch in dogs. Res Commun Chem Pathol Pharmacol 36:199, 1982
29a. Schmand JF, Ayala A, Morrison MH, et al. Effects of hydroxyethyl starch after trauma-hemorrhagic shock; Restoration of macrophage integrity and prevention of increased circulating interleukin-6 levels. Crit Care Med 23:806, 1995
29b. Mishler JM. Pharmacology of hydroxyethyl starch. Use in therapy and blood banking. Oxford, Oxford University Press, 1982
30. Thompson WL, Walton RP. Blood changes, renal function and tissue storage following massive infusion of hydroxyethyl starches; abstract. Fed Proc 22:640, 1963
31. Rackow EC, Weil MH, Macneil AR. Effects of crystalloid and colloid fluids on extravascular lung water in hypoproteinemic dogs. J Appl Physiol 62:2421, 1987
32. Heidenreich O, Muhlen K, Heintze K. The effect of the plasma substitutes hydroxyethyl starch and dextran 60 on the kidney function of dogs in acute hemorrhagic shock. Anaesthetist 24:239, 1975
33. Rajagopalan ER, Reines HD, Pulliam C, et al. Reversal of acute renal failure using hemodilution with hydroxyethyl starch. J Trauma 23:795, 1983
34. Murphy GP, Demaree DE, Gagnon JA. The renal and systemic effects of hydroxyethyl starch solution infusions. J Urol 93:534, 1965
35. Strauss RG, Stump DC, Henriksen RA. Hydroxyethyl starch accentuates von Willebrand's disease. Transfusion 25:235, 1985
36. Smiley LE. The use of hetastarch for plasma expansion. *In* Hohenhaus AE (ed). Problems in Vet Med (Transfusion Medicine) 4:652, 1992
37. Thompson WL, Walton RP. Circulatory responses to intravenous infusions of hydroxyethyl starch solutions. J Pharmacol Exp Ther 146:359, 1964
38. Grubber UP. Blood Replacement. New York, Springer-Verlag, 1969
39. Concannon KT, Haskins SC, Feldman BF. Hemostatic defects associated with two infusion rates of dextran 70 in dogs. Am J Vet Res 53:1369, 1992
40. Mooney SA. Preparation of blood components. *In* Hohenhaus AE (ed). Problems in Vet Med (Transfusion Medicine) 4:594, 1992
41. Rainey TG, Read CA. Pharmacology of colloids and crystalloids. *In* Chernow B (ed). The Pharmacologic Approach to the Critically Ill Patient. 3rd ed. Baltimore, Williams & Wilkins, 1994, pp 272–290
42. Rothschild MA, Oratz M, Schreiber SS. Albumin synthesis. N Engl J Med 286:748, 1972
43. Rothschild MA, Oratz M, Franklin EC, et al. The effect of hypergammaglobulinemia on albumin metabolism in hyperimmunized rabbits studied with albumin-I131. J Clin Invest 41:1564, 1962
44. Emerson TE. Unique features of albumin: A brief review. Crit Care Med 17:690, 1989
45. Hardie EM. Sepsis versus septic shock. *In* Murtaugh RJ, Kaplan PM (eds). Veterinary Emergency and Critical Care Medicine. St Louis, CV Mosby, 1992, p 176
46. Pichler ME, Turnwald GH. Blood transfusion in the dog and cat. Part I: Physiology, collection, storage and indications for whole blood therapy. Comp Cont Educ Vet 7:64, 1985
47. Smith CA. Transfusion medicine: The challenge of practical use. J Am Vet Med Assoc 198:747, 1991
48. Marion RS, Smith JE. Survival of erythrocytes after autologous and allogenic transfusions in cats. J Am Vet Med Assoc 183:1437, 1983
49. Giger U, Bucheler J. Transfusion of type-A and type-B blood to cats. J Am Vet Med Assoc 198:411, 1991
50. Giger U. Feline transfusion medicine. *In* Hohenhaus AE (ed). Problems in Vet Med (Transfusion Medicine) 4:600, 1992

51. Giger U, Kilran CG, Filippich LJ, et al. Frequencies of feline blood groups in the United States. J Am Vet Med Assoc 195:1230, 1989
52. Giger U, Bucheler J, Patterson DF. Frequency and inheritance of A and B blood types in feline breeds of the United States. J Heredity 82:15, 1991
53. Callan MB, Giger U. Transfusion medicine. *In* August JR (ed). Consultations in Feline Internal Medicine. Philadelphia, WB Saunders, 1993
54. Kristensen AT, Feldman BF. Blood banking and transfusion medicine. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 347
55. Hohenhaus AE. Canine blood transfusion. *In* Hohenhaus AE (ed). Problems in Vet Med (Transfusion Medicine) 4:612, 1992
56. Rentko VT. Red blood cell substitutes. *In* Hohenhaus AE (ed): Problems in Vet Med (Transfusion Medicine) 4:647, 1992
57. Sprung CL. The Pulmonary Artery Catheter. Baltimore, University Park Press, 1983
58. Shoemaker WC, Appel PL, Kram HB, et al. Comparison of hemodynamic and oxygen transport effects of dobutamine and dopamine in critically ill surgical patients. Chest 96:120, 1989
59. Lollgen H, Drexler H. Use of inotropes in the critical care setting. Crit Care Med 18:S56, 1990
60. Zaritsky AL. Catecholamines, inotropic medications, and vasopressor agents. *In* Chernow B (ed). The Pharmacologic Approach to the Critically Ill Patient. 3rd ed. Baltimore, Williams & Wilkins, 1994, p 387
61. Driscol DJ, Gillete PC, Exrailson EG. Inotropic responses of the neonatal canine myocardium to dopamine. Pediatr Res 12:42, 1978
62. Maekawa K, Liang CS, Hood WB. Comparison of dobutamine and dopamine in acute myocardial infarction. Circulation 67:750, 1983
63. van Kesteren RG, van Alphen MMA, Charbon GA. Effects of dopamine on intestinal vessels in anesthetized dogs. Circ Shock 25:41, 1988
64. Marino RJ, Romagnoli A, Keats AS. Selective venoconstriction by dopamine in comparison with isoproterenol and phenylephrine. Anesthesiology 43:570, 1975
65. Whitfield I, Sowers JR, Tuck MI, Golub MS. Dopaminergic control of plasma catecholamine and aldosterone response to acute stimuli in normal man. J Clin Endocrinol Metab 51:724, 1980
66. Ruffolo RR Jr, Sporadlin TA, Pollock GD, et al. Alpha- and beta-adrenergic effects of the stereoisomers of dobutamine. J Pharmacol Exp Ther 219:447, 1981
67. Fox PR. Feline myocardial diseases. Proceedings of the 18th Annual Waltham/OSU Symposium: Cardiology. Vernon, California, Waltham USA, Inc, 1994, p 117
68. Hardie EM, Rawlings CA, Calvert CA. Severe sepsis in selected small animal surgical patients. J Am Anim Hosp Assoc 22:33, 1986
69. Hirsh DC, Jang SS, Biberstein EL. Blood culture of the canine patient. J Am Vet Med Assoc 184:175, 1984
70. Dow SW, Jones RL, Adney WS. Anaerobic bacterial infections and response to treatment in dogs and cats: 36 cases (1983–1985). J Am Vet Med Assoc 189:930, 1986
70a. Jang SS, Breher JE, Dabaco LA, et al. Organisms isolated from dogs and cats with anaerobic infections and susceptibility to selected antimicrobial agents. J Am Vet Med Assoc 210:1610, 1997
71. Olin BR (ed). Drug Facts and Comparisons. Philadelphia, JB Lippincott, 1991, p 1530
72. Brown SA. Treatment of gram-negative infections. Vet Clin North Am 18:1141, 1988
73. Dow SW. Management of anaerobic infections. Vet Clin North Am 18:1167, 1988
74. Donowitz GR, Mandell GL. Beta-lactam antibiotics. Engl J Med 318:419, 1988
75. Papich MG. Therapy of gram-positive bacterial infections. Vet Clin North Am 18: 1167, 1988
76. Kilgore WR. Clavulanate-potentiated antibiotics. *In* Kirk RW (ed). Current Veterinary Therapy X. Philadelphia, WB Saunders, 1989, p 78
77. Riviere JE. Cephalosporins. *In* Kirk RW (ed). Current Veterinary Therapy X. Philadelphia, WB Saunders, 1989, p 74
78. Karam GH. New antibiotics in the critical care unit. Crit Care Rep 2:128, 1991
79. Longhofer SL. Chemotherapy of rickettsial, protozoal, and chlamydial diseases. Vet Clin North Am 18:1183, 1988
80. Altura BM, Altura BT. Peripheral vascular actions of glucocorticoids and their relationship to protection in circulatory shock. J Pharmacol Exp Ther 190:300, 1974
81. Altura BM. Glucocorticoid-induced protection in circulatory shock. Role of reticuloendothelial system function. Proc Soc Exp Biol Med 150:202, 1975
82. Vargish T, Turner CS, Bond RF, et al. Dose-response relationships in steroid therapy for hemorrhagic shock. Am Surg 43:30, 1977
83. Sprung CL, Caralis PV, Marcial EH. The effects of high-dose corticosteroids in patients with septic shock. N Engl J Med 311:1137, 1984
84. Veterans Administration Systemic Sepsis Cooperative Study Group: Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. N Engl J Med 317:659, 1987
85. Bone RC, Fisher CJ, Clemmer TP, et al. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 317:653, 1987
86. Luce JM, Montgomery AB, Marks JD, et al. Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. Am Rev Respir Dis 138:62, 1988
87. White GL, White GS, Kosanke SD, et al. Therapeutic effects of prednisolone sodium succinate vs. dexamethasone in dogs subjected to *E. coli* septic shock. J Am Anim Hosp Assoc 18:639, 1982
88. Schumer W. Steroids in the treatment of clinical septic shock. Ann Surg 184:333, 1976
89. Hoffman SL, Punjabi NH, Kumala S, et al. Reduction of mortality in chloramphenicol-treated severe typhoid fever by high-dose dexamethasone. N Engl J Med 310:82, 1984
89a. Bollaert P-E, Charpentier C, Levy B, et al. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med 26:645, 1998
90. Beck RR, Abel FL, Papadakis E. Influence of ibuprofen on renal function in acutely endotoxemic dogs. Circ Shock 28:37, 1989
91. Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 100:483, 1984
92. Arvidsson S, Falt K, Haglund U. Acute gastric mucosal ulceration in septic shock. Acta Chir Scand 150:541, 1984
93. Arvidsson S, Falt K, Haglund U. Feline *E. coli* bacteremia—effects of misoprostol/scavengers or methylpred-

nisolone on hemodynamic reactions and gastrointestinal mucosal injury. Acta Chir Scand 156:215, 1990
94. Fowler AA, Hamman RF, Good TJ, et al. Adult respiratory distress syndrome: Risk with common predispositions. Ann Intern Med 98:593, 1883
95. Green RA, Thomas JS. Hemostatic disorders: Coagulopathies and thrombosis. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 1946
96. Minard G, Kudsk KA. Is early feeding beneficial? How early is early? New Horizons 2:156, 1994
97. Zimmerman JJ. Oxygen free radicals. *In* Chernow B (ed). The Pharmacologic Approach to the Critically Ill Patient. Baltimore, Williams & Wilkins, 1994, p 901

16

Electrophysiologic Mechanisms for Arrhythmias

KENNETH H. DANGMAN

Research on the electrophysiology of arrhythmias has evolved through several phases. The first phase started in the 1890s, when extracellular recording techniques were developed to detect body surface electrocardiograms and direct electrograms from the myocardium. Use of these techniques led to the recognition of several types of arrhythmias as well as description of two basic mechanisms for tachycardias in the atria or ventricles: ectopic automaticity and re-entrant activity. The second phase of research started in the late 1940s, with the development of intracellular recording techniques. These used potassium chloride–filled microelectrodes coupled to high-input impedance amplifiers to detect transmembrane action potentials (Fig. 16–1) from single cardiac cells in tissue preparations. The third phase began in the early 1980s, with the development of patch clamp techniques or cloned ion channels for the study of transmembrane ionic currents of enzymatically isolated myocytes.[1]

Cardiac electrophysiology has been investigated intensively over the past 100 years. Many of these studies used experimental animals with normal hearts or with induced pathology and arrhythmias. Therefore, the insights and conclusions gained from these studies are relevant to veterinary medicine.

ELECTROPHYSIOLOGY OF THE NORMAL HEART

It is necessary to understand normal cardiac function before considering the pathophysiology that can lead to arrhythmias. In the healthy individual, the heart remains in sinus rhythm (in many dogs, sinus arrhythmia predominates), which appears on the surface electrocardiogram as a regular, repeating sequence of three deflections or waveforms (Fig. 16–2). These three deflections are the P, the QRS, and the T wave. The normal cardiac impulse begins in the sinus node, which is also called the sinoatrial or SA node. In beagle dogs the node is up to 40 mm long and is found at the rostral junction of the anterior vena cava and the right atrium. The transmembrane potential of the sinus node pacemaker cells gradually decreases during diastole until threshold potential is attained (see Fig. 16–2). The specific pacemaker site can vary slightly; changes in autonomic tone and heart rate may shift the pacemaker within the node.

Diastolic depolarization in the sinus node begins from a maximum potential of about −60 millivolts (mV), and it is thought to be produced by decay

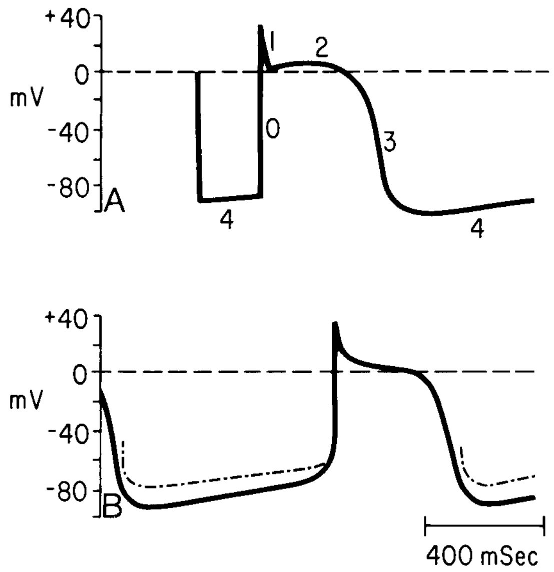


FIGURE 16–1

Diagrams of transmembrane action potentials. In both panels, the heavy line shows output of the microelectrode. Dashed line shows zero or extracellular reference potential. The voltage level (in millivolts) is shown along the vertical axis. Note time bar at lower right.

Upper panel: Initially, the voltage level is zero when the tip of the electrode is in extracellular fluid. As the cell is impaled, the voltage reading reflects intracellular potential. During diastole, the transmembrane potential is about −90 mV. When an action potential occurs, the polarization of the membrane reverses; the transmembrane potential transiently spikes at +35 to +40 mV. This rapid upstroke is called phase 0 (zero). Repolarization occurs in three phases: phase 1 is the rapid repolarization phase that occurs 1 to 5 msec after the spike. Phase 2 is the slow repolarization that occurs during the action potential plateau. Phase 3 is the moderately rapid repolarization that occurs at the end of the plateau that carries the potential to diastolic levels (phase 4).

Lower panel: Spontaneously firing Purkinje fiber. Pacemaker activity in the heart occurs when phase 4 depolarization slowly carries membrane potential to the threshold voltage for inward current. Threshold voltage during diastole is shown here as a dashed line above the transmembrane potential. This pacemaker activity normally occurs in the SA node (see Fig. 16–2), and, if overdrive from the SA node is relieved, in subsidiary pacemaker tissues such as specialized atrial conduction tissue and ventricular Purkinje fibers (shown here).

of a current "i_K", which is an outward current carried by potassium ions, or by onset of an inward current "i_f", which is carried by sodium and potassium ions.[2] The upstroke of the sinus node action potential occurs when diastolic depolarization carries the membrane potential to the voltage thresholds for the onset of two inward calcium currents ("i_{Ca-T}" and then "i_{Ca-L}"). Sinus node depolarization, occurring as it does in a relatively small mass of tissue, is not reflected on the surface electrocardiogram.

After the pacemaker cell fires an action potential, the impulse conducts slowly throughout the sinus node and then spreads to the adjacent cells of the atrial myocardium. Once in the myocardium, the impulse propagates radially through the tissues of the right and left atria. Normal atrial muscle fibers have relatively high action potential amplitudes (100 to 110 mV) and maximum upstroke velocities (100 to 200 V/sec). The upstroke is carried by the *fast Na^+ current* (i_{Na}). The impulse is conducted fairly quickly throughout the atria. The wavefront of atrial depolarization produces the P wave of the electrocardiogram (see Fig. 16–2).

The wavefront of the cardiac impulse is conducted from atrial tissues to the atrioventricular (AV) node. The wavefront of excitation may spread to the AV node via specialized pathways (called the *anterior, middle,* and *posterior internodal tracts*) in the right atrium. They carry the impulses preferentially to the AV node. They may be responsible for sinoventricular conduction. That is, sometimes during hyperkalemia no P wave occurs, but the sinus node will continue to fire and regularly activate the ventricles.

The atrioventricular node is specialized to provide slow conduction. The nodal cells are small and relatively poorly coupled electrically. The transmembrane action potentials of the nodal cells have low amplitudes (60 to 80 mV) and slow upstroke velocities (5 to 10 volts/second [V/sec]), and they arise from relatively low diastolic potentials (about −60 mV). The upstrokes of the action potentials are carried by the *slow inward* or *calcium current* (i_{Ca}), rather than the fast sodium current. As a result of the slow conduction,

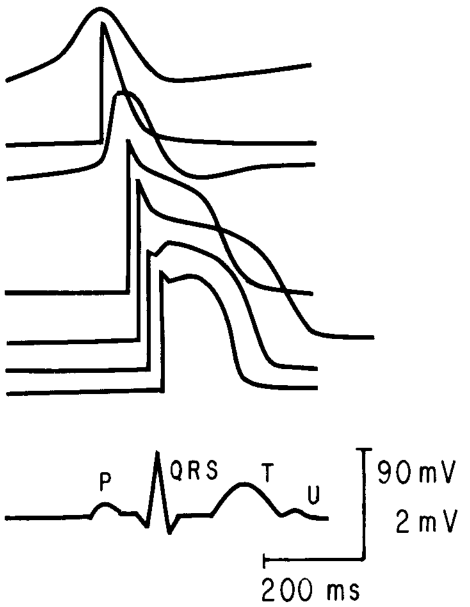


FIGURE 16–2

Diagram of transmembrane action potentials in atrial and ventricular tissues during normal sinus rhythm. Traces, from top to bottom, show action potentials of a sinus node cell, atrial myocardial fiber, AV node cell, His bundle fiber, distal Purkinje fiber, endocardial ventricular muscle cell, and epicardial ventricular muscle cell. The lowermost trace shows the surface electrocardiogram. Note time and voltage calibration bars at the lower right. The voltage calibration bar is 2 mV for the electrocardiogram (ECG), 90 mV for action potentials.

the wavefront of the cardiac impulse propagates slowly through the AV node. The slow conduction allows an appropriate interval (60 to 130 msec in the canine heart, 50 to 90 msec in the feline heart) to elapse between atrial and ventricular contraction.

When the impulse emerges from the distal end of the AV node, it invades the Purkinje fibers of the proximal His bundle. These Purkinje fibers have high diastolic potentials (about −90 mV), action potential amplitudes of 110 to 140 mV, and maximum rates of depolarization (200 to 1000 V/sec).[3] Depolarization of the cells of the atrioventricular node and the Purkinje system does not produce a waveform on the surface electrocardiogram. Extracellular recording of Purkinje fiber activity is possible, however, using an intracardiac catheter to detect the His bundle electrogram.

Once the cardiac impulse enters the His bundle, it is rapidly propagated through the ventricular conduction system to the distal Purkinje fibers on the endocardial surfaces of both ventricles. The distal Purkinje fibers conduct the impulse to the subendocardial ventricular muscle. Propagation in the myocardium then progresses to the subepicardial layers. Ventricular excitation gives rise to the QRS deflection of the surface electrocardiogram.

After each impulse is conducted to the outermost layers of the ventricular walls, it is extinguished as the wavefront becomes surrounded with refractory or inexcitable tissues. The final event of the cardiac electrical cycle is ventricular repolarization. It produces the T wave and, rarely, a U wave (see Fig. 16–2).

ELECTROPHYSIOLOGIC EFFECTS OF CARDIAC DAMAGE: GENERAL CONSIDERATIONS

Cardiac arrhythmias rarely occur in normal hearts but often occur in hearts with structural degeneration or acute injury. Most myocardial lesions (including ischemia, anoxia, metabolic inhibition, stretch, digitalis toxicity, myocardial infarction, congestive heart failure, and cardiomyopathies) will change cardiac action potentials in characteristic ways. These effects, as explained later, can lead to ectopic impulses, tachycardias, or fibrillation.

DECREASES IN DIASTOLIC MEMBRANE POTENTIAL

Typically, diastolic membrane potential is −80 to −90 mV in ventricular or atrial muscle cells and −85 to −95 mV in Purkinje fibers. Generally, these diastolic potential levels will decrease (i.e., become less negative) after myocardial damage. The decreases in diastolic potential that occur in these injured cells may result from (1) decreased activity of the sarcolemmal Na^+–K^+ ATPase (the electrogenic "sodium pump," which provides a net outward pump current as a result of the asymmetric transport of cations); (2) increased inward sodium conductance (G_{Na}); and (3) decreased outward potassium conductance (G_K).

These changes tend to increase net inward current, and therefore to depolarize the cell. In addition, decreased electrogenic sodium pump activity will increase intracellular Na^+ concentrations, decrease intracellular K^+ concentrations, and increase K^+ concentrations in the interstitial clefts of the myocardium. These changes in concentrations of K^+ and Na^+ can help reduce the level of diastolic transmembrane potential by decreasing the magnitude of the electrochemical ionic gradients across the cell membrane.

When diastolic potential in working myocardial or Purkinje fibers decreases significantly, voltage-dependent changes will occur in cellular electrical activity. Reduced membrane potential can induce abnormal automaticity or triggered activity, or it can slow propagation of the cardiac impulse and lead to conduction block and/or re-entrant excitation.

DECREASES IN THE AMPLITUDE AND RATE OF RISE OF PHASE 0

The effects of decreases in diastolic potential on conduction are largely explainable through effects on phase 0 of the action potential (Fig. 16–3). In myocardial fibers (for membrane potentials between −60 mV and −90 to −100 mV), conduction velocity is directly proportional to take-off potential. This is because the amplitude and maximum rate of depolarization of phase 0 are important determinants of conduction velocity. Simply stated, action potentials with higher amplitudes and faster depolarization rates provide a better stimulus for induction of the regenerative response (the upstroke of the action potential) in downstream areas of membrane that are resting in the diastolic voltage ranges. Thus, more distal membrane areas will be brought to threshold level more quickly by a robust action potential than by a depressed action potential. Therefore, the robust impulse will be conducted more rapidly.

The amplitude and depolarization rate of phase 0 in turn are largely dependent on the intensity of the rapid inward sodium current. The inward sodium current is carried through ion-selective *channels* in the cell membrane.[4] These channels are guarded by *gates* that impede ion fluxes; the opening and closing of these gates is both voltage- and time-dependent.[4] It is thought that as the take-off potential becomes less and

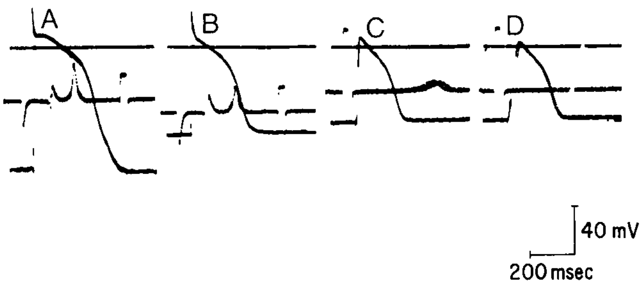


FIGURE 16–3

Effects of a decrease of resting membrane potential in a Purkinje fiber by elevation of extracellular potassium. Each panel shows a transmembrane action potential from a canine Purkinje fiber, the zero reference potential (horizontal line) for the action potential, and a differentiated signal obtained during the upstroke of the action potential. The horizontal placement of the differential trace is arbitrary. The peak of this differential recording is the maximal upstroke velocity of the action potential (dV/dt_{max}). The differentiated trace also shows a square wave in each panel; this is a 200 V/sec calibration signal. Note that the gain on the differential amplifier is lower in *A* and *B* than in *C* and *D*. *A* shows the control action potential in Tyrode's solution (physiologic saline) containing 2.7 mM of potassium chloride (KCl); maximum diastolic potential (MDP) is −92 mV, and dV/dt_{max} is 322 V/sec. In *B*, the KCl level is about 10 mM; the resting membrane potential is −66 mV, and the dV/dt_{max} is 200 V/sec. In *C*, the diastolic membrane potential is −58 mV, and the dV/dt_{max} shows two upstrokes of 20 to 26 V/sec. In *D*, the diastolic membrane potential is −55 mV, and the action potential became a slow response. No dV/dt_{max} could be determined; at rates under 5 V/sec, the deflection in the differential trace is too small to be measured. Shortly after this final photograph was taken, the membrane potential decreased slightly more, and no further action potentials were elicited.

less negative, more and more of the sodium channels become *inactivated* (i.e., totally refractory to stimulation). Thus, as the take-off potential is decreased from −90 to about −60 mV, the sodium current during phase 0 becomes less and less robust, the amplitude and rate of rise of the action potential are reduced, and the conduction velocity is decreased (Fig. 16–3).

The term *depressed fast responses* describes action potentials occurring in partially depolarized myocardial cells with take-off potentials between −75 and −60 mV. Depressed fast responses may be important in the genesis of re-entrant arrhythmias. This is because the depressed fast responses will propagate more slowly than normal action potentials, and this will facilitate the occurrence of re-entry (see later). Also, if the impulse must traverse a zone of relatively inexcitable tissue, the depressed fast response, having an intrinsically lower stimulus efficacy than the normal responses, will be more prone to allow conduction blocks to occur.

Many of the Class I antiarrhythmic drugs (e.g., lidocaine, procainamide, and bepridil) decrease upstroke and conduction velocity in cells with depressed fast responses in therapeutic (low) concentrations, and these concentrations do not affect normal action potentials.[5–7] This selective action may convert a zone of unidirectional conduction block to a zone of bidirectional block and thus disrupt a re-entrant circuit. Therefore, local anesthetic effects on depressed fast responses may underlie important antiarrhythmic actions of these drugs.

When the take-off potential is reduced to a value less than −60 mV, the fast inward sodium channels are largely, if not entirely, inactivated. Yet action potentials still may occur in fibers with diastolic potentials of −55 to −35 mV. These action potentials, which are referred to as "slow responses",[8] will be generated if sufficient *slow inward* or *type L-calcium current* ($i_{Ca\text{-}L}$) can be elicited.[9] The upstroke velocity of phase 0 of the slow response action potentials is in the range of 1 to 5 V/sec, and so they are conducted very slowly (i.e., 0.02 to 0.05 meters/sec). Obviously, the slow responses will provide less effective stimuli for regenerative responses than normal or depressed fast responses. Therefore, slow response–dependent action potentials are very likely to show variable conduction rates and unidirectional or bidirectional block. Partially depolarized myocardial tissues generating slow responses also provide the anatomic substrate for re-entrant arrhythmias.

Not all cardiac cells with resting potentials positive to −60 mV will support slow responses. This is because $i_{Ca\text{-}L}$ can be a weak current; if appreciable outward (i.e., potassium) current is flowing, slow responses may not be elicited. In these circumstances, augmenting $i_{Ca\text{-}L}$ may lead to slow response action potentials. Phosphorylation of an internal site on one of the subunit proteins of the slow inward channel enhances $i_{Ca\text{-}L}$; a cyclic AMP-dependent protein kinase catalyzes this phosphorylation. Therefore, catecholamines and phosphodiesterase inhibitors (caffeine, theophylline, and milrinone) can induce slow response action potentials. Thus, it is possible that arrhythmias caused by β-adrenergic stimulation or increased sympathetic tone may be associated with slow response action potentials. The specific mechanisms involved are described later.

It is likely that both slow response and depressed fast response action potentials can be found within or around the zone of pathology in most diseased hearts. It is not likely that any type of cardiac damage, whether focal or diffuse, will produce an abrupt and totally uniform decrease in diastolic transmembrane potential throughout the affected area. Some cells may have take-off potentials of −60 to −75 mV, partially inactivated fast sodium channels, and depressed fast responses. Other cells may have take-off potentials of less than −60 mV and completely inactivated sodium channels. Some of these cells may support relatively robust slow response action potentials and very slow conduction, whereas other highly depolarized cells may show tenuous slow responses with decremental conduction and block. Finally, some of the highly depolarized cells may have sufficiently strong outward

(potassium) currents and weak inward (calcium) currents such that they do not support any regenerative responses at all. Obviously, a zone of these highly depolarized fibers could produce a site of either unidirectional or bidirectional conduction block.

DECREASES IN ACTION POTENTIAL DURATION AND REFRACTORINESS

Many cardiac diseases result in changes in action potential duration; either decreases or increases can occur. These changes in action potential duration can be important for arrhythmogenic mechanisms because recovery of excitability in normal atrial and ventricular myocardial cells accompanies repolarization (during phase 3 of the action potential). That is, excitability begins to recover after the cell has repolarized to about −60 mV; the upstroke velocities of a premature action potential then increase more and more as the take-off potential increases during the terminal portion of phase 3. Recovery of excitability is complete in normal myocardial cells or Purkinje fibers when maximum diastolic potential (or full diastolic potential) is achieved. Complete recovery of excitability occurs when the maximum rate of depolarization and action potential amplitude of a premature action potential are essentially identical to those of the control action potentials elicited at the basic cycle length (Fig. 16–4). This rapid recovery of excitability is referred to as *voltage-dependent refractoriness.*

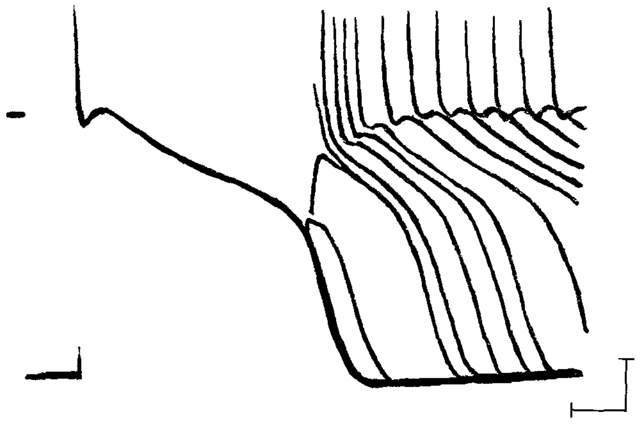


FIGURE 16–4

Example of voltage-dependent refractoriness in a record obtained in a sheep Purkinje fiber preparation. Premature action potentials elicited at 14 different coupling intervals after primary beat are shown; the primary beat is shown at the left. Early premature impulses occurring during phase 3 of the primary action potential produce only local responses. As fiber repolarizes, premature beats abruptly attain more normal amplitudes. At the beginning of phase 4, premature impulses have essentially normal amplitude (4th premature upstroke from left). Amplitude and upstroke velocity do not increase further as the impulses are moved later and later into diastole. Note calibration bars at lower right: vertical represents 20 mV; horizontal, 100 msec.

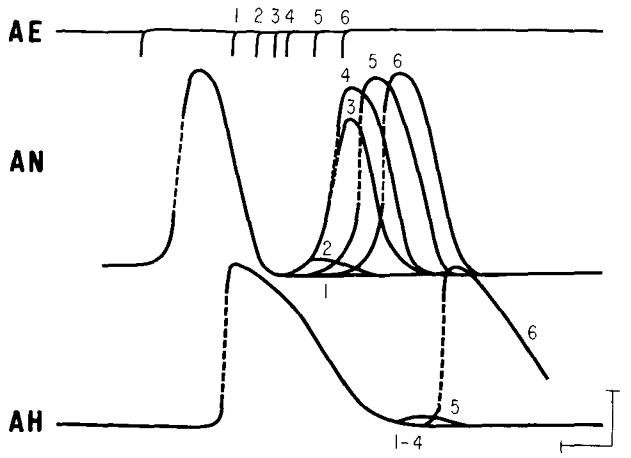


FIGURE 16–5

Example of time-dependent refractoriness in a record in a rabbit AV node preparation. Each trace shows superimposed electrograms or action potentials for the primary beat and one of the six premature beats that were elicited at increasing coupling intervals. The upper trace shows the atrial electrogram (AE); the middle trace shows action potentials recorded from a cell in the proximal region of the node (AN region). The lower trace (AH) shows the record from the distal region of the node. Note that the only premature impulse to propagate through the node is number 6; premature impulse number 5 produces only a subthreshold response, and numbers 1 to 4 produce no effect at the distal node. In the AN cell, premature impulse number 6 produces a normal action potential. Earlier impulses produce less and less response in the AN region, even though they arrive at the node after this region has fully repolarized. This is time-dependent refractoriness. Note calibration bars at lower right; vertical bar is 25 mV; horizontal bar, 50 msec. (Diagram based on original records from Mendez C, Moe GK. Some characteristics of transmembrane potentials of AV nodal cells during propagation of premature beats. Circ Res 19:993, 1966. Copyright 1966 American Heart Association.)

In cardiac tissues with take-off potentials more positive than about −70 mV, either depressed fast responses or slow response action potentials will occur. In these tissues, refractoriness can be a function of time as well as of voltage. That is, recovery of the amplitude and maximum rate of depolarization of a premature impulse extends well into phase 4 (Fig. 16–5). The different rates of recovery of excitability in normal and depressed segments of isolated canine Purkinje fibers are known to produce rate-dependent block[8] and are thought to underly re-entrant arrhythmias in canine ventricle.

SPECIFIC MECHANISMS FOR CARDIAC ARRHYTHMIAS

Much is known about the cellular mechanisms of arrhythmic activity in the mammalian heart.[9] Arrhythmias can be caused by abnormalities of impulse initiation, impulse conduction, or both.[10, 11] Table 16–1 shows a simple classification system for these cellular mechanisms.

TABLE 16–1
Electrophysiologic Mechanisms of Ventricular Arrhythmias

A. Arrhythmias caused by enhanced impulse initiation in ectopic foci:
  1. Automatic rhythms:
    a. Normal Purkinje fiber automaticity (MDP > −70 mV)
    b. Catecholamine-enhanced automaticity in normal Purkinje fibers
    c. Abnormal automaticity (MDP < −60 mV) in Purkinje fibers and ventricular muscle cells
  2. Triggered rhythms:
    a. Early afterdepolarizations
    b. Delayed afterdepolarizations
B. Arrhythmias caused by abnormal impulse conduction:
  1. Conduction blocks
  2. Re-entrant activation:
    a. Macro re-entry
      (1) Fixed pathway/anatomic barrier
      (2) Variable pathway/"leading circle"
    b. Micro re-entry
      (1) Functional longitudinal dissociation
      (2) Reflection
C. Arrhythmias caused by simultaneous derangements of impulse initiation and impulse conduction:
  1. Parasystole
  2. Complex arrhythmias

MDP, Maximum diastolic potential.

ARRHYTHMIAS CAUSED BY ENHANCED IMPULSE INITIATION IN ECTOPIC FOCI

Ectopic arrhythmias caused by enhanced impulse initiation are generated by a specific cell (or small group of cells that are well coupled electrically) outside of the sinus node. This cell or group of cells is referred to as the "focus" of the arrhythmia, and generally is found in the zone of earliest activation during the ectopic beats. The cells in the focus have action potentials with a characteristic "pacemaker" configuration (Fig. 16–6). That is, they undergo rapid phase 4 depolarization that gradually leads to a regenerative response; a sharp inflection point at the foot of phase 0 is not seen. The presence of pacemaker fibers in a distinct ectopic focus distinguishes arrhythmias caused by *enhanced impulse initiation* from other arrhythmias such as those caused by conduction block and/or re-entrant activation.[12] The two subtypes of arrhythmias caused by enhanced impulse initiation are automatic rhythms and triggered rhythms.[8]

AUTOMATIC RHYTHMS

Arrhythmias caused by automaticity occur when a subsidiary pacemaker site in the atria or ventricles becomes active and fires at a rate faster than that of the sinus node. *Automaticity* is defined as spontaneous impulse generation occurring from a discrete pacemaker site that, as opposed to *triggering,* does not depend on previous activation of that site for its initiation.[8] Pacemaker activity can result from either normal automaticity or abnormal automaticity.

Normal automaticity occurs spontaneously in nonpathologic tissues, such as the sinus node, and subsidiary pacemaker cells of the atria (specialized atrial conduction fibers) and the ventricular conduction system. In ventricular tissues, normal automaticity occurs only in Purkinje fibers, with maximum diastolic potentials of about −70 mV or more and upstrokes carried by the fast inward sodium current. *Abnormal automaticity* occurs in Purkinje fibers and working myocardial cells with markedly depolarized (approximately −55 mV) maximum diastolic potentials and upstrokes carried by i_{Ca-L}.

There are at least two types of normal automaticity: (1) normal automaticity in sinus node pacemakers occurs from maximum diastolic potentials of about −60 mV and resembles abnormal automaticity in that the upstrokes are carried by a calcium current; (2) in contrast, normal automaticity in Purkinje fibers occurs by a different mechanism, as described next.

NORMAL AUTOMATICITY IN PURKINJE FIBERS. Normal automaticity in canine, feline, and primate Purkinje fi-

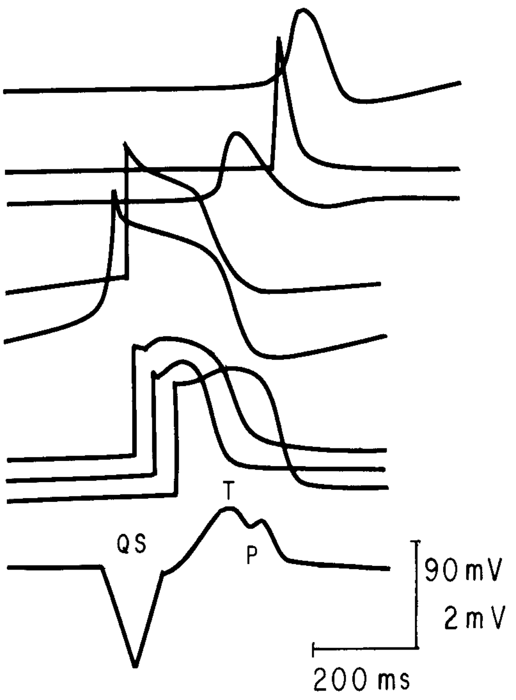


FIGURE 16–6

Representation of the sequence of depolarization during a ventricular ectopic beat. Format as in Figure 16–2. Arrhythmia occurs because the ectopic pacemaker in the distal Purkinje fiber (5th action potential from the top) is firing rapidly. The His bundle, AV node, atrial muscle, and SA node all are activated in retrograde direction; the ventricular muscle is activated in an aberrant sequence. This results in a premature ventricular depolarization; note the longer QRS duration with altered vectors, and the retrograde P wave superimposed on the T wave in the electrocardiogram *(bottom trace).*

bers denotes spontaneous impulse initiation from normal maximum diastolic potentials (-70 to -95 mV). It occurs when overdrive from higher pacemakers is relieved (Fig. 16–7*A*). The diastolic depolarization responsible for normal automaticity is generated by a net inward ionic current that reflects a balance of inward and outward currents.[13] Although the detailed behavior of these currents is not entirely clear, at least four factors may contribute to the voltage time course of diastole in the normally automatic cardiac cell: (1) an inward current (i_f), which is carried by Na^+ and K^+ ions, and which shows voltage and time dependence; (2) an outward current carried by potassium, which shows voltage dependence but is now thought not to have time dependence; (3) an outward current generated by activity of the electrogenic Na^+-K^+ ATPase (the "sodium pump"); and (4) the threshold voltage and onset characteristics of the fast inward (sodium) current that generates the upstroke of the action potential. Thus, normal automaticity in Purkinje fibers is a very complex phenomenon.[14]

Antiarrhythmic drugs can reduce normal automatic rhythms directly by (1) decreasing the slope of diastolic depolarization, (2) increasing the threshold potential for the fast inward current, (3) increasing the maximum diastolic potential, or (4) a combination of these effects. Antiarrhythmic drugs also can alter rate and rhythm of the heart indirectly, by interacting with autonomic nervous system reflexes or circulatory catecholamines.

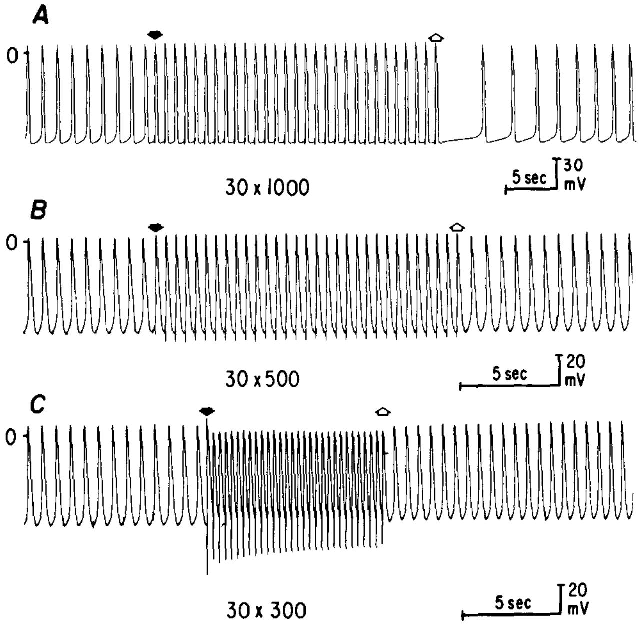


FIGURE 16–7

Effects of overdrive stimulation on normal and abnormal automaticity in canine Purkinje fibers. Panel *A* shows the effects of 30 beats at a cycle length of 1000 msec (60 bpm) on a normal preparation with maximal diastolic potential in the pacemaker region of about -90 mV. Post-overdrive suppression occurs after cessation of the stimulus train. Panels *B* and *C* show effects of overdrive on fibers with abnormal automaticity. Neither overdrive hyperpolarization nor post-overdrive suppression of automaticity occurs. Note different time and voltage calibrations (shown below each panel) for panels *B* and *C* versus panel *A*. (Reprinted with permission of the American College of Cardiology, from Dangman KH, Hoffman BF. Studies on overdrive stimulation of canine cardiac Purkinje fibers: Maximal diastolic potential as a determinant of the response. Reprinted by permission of the American College of Cardiology. J Am Coll Cardiol 2:1183, 1983.)

ABNORMAL AUTOMATICITY. Abnormal automaticity is thought to be an important cause of atrial and ventricular arrhythmias.[15] It is a form of rapid ectopic impulse initiation that occurs in working myocardial cells or Purkinje fibers with maximum diastolic potentials in the range of -60 to -40 mV (Fig. 16–8). It can arise after cardiac tissues have been damaged by ischemia, stretch, or drug toxicity (e.g., digitalis). The mechanisms of abnormal automaticity may be simpler than those involved in normal automaticity, because abnormal automaticity occurs in a diastolic voltage range in which beat-to-beat activation of the fast inward (sodium) current is neglible during the action potential upstroke. Because the sodium influx is minimal in the partially depolarized cells, the electrogenic sodium pump will make a very small contribution to the diastolic voltage changes of abnormal automaticity. Thus, in contrast to normal Purkinje fibers, abnormal automatic pacemakers do not show post-overdrive suppression following a period of rapid stimulation (Fig. 16–7*B*, *C*).

Diastolic depolarization in abnormal automaticity has been attributed to a time-dependent decrease of outward potassium current[9, 16] or to the inward pacemaker current i_f.[17] As mentioned earlier, the action potentials in abnormal automaticity are slow responses carried by an inward calcium current (i_{Ca-L}). It can be abolished by Class IV antiarrhythmic drugs such as verapamil and nifedipine.[18] As in normal automaticity, drugs can slow or abolish abnormal automaticity directly by (1) decreasing the slope of diastolic depolarization, (2) increasing the threshold potential for calcium current, (3) increasing the maximum diastolic potential, or (4) some combination of these factors. Antiarrhythmic drugs also may alter abnormal automaticity by indirect effects (i.e., occurring through interactions with the autonomic nervous system).

TRIGGERED ACTIVITY

This second type of ectopic impulse generation occurs from a discrete pacemaker site.[8] Triggered activity may be paroxysmal or continuous, but it occurs if and only if the pacemaker has previously been driven by an appropriate action potential or series of action potentials. That is, in contrast to automatic rhythms (which occur *de novo*), triggered rhythms occur only after an initiating beat that produces depolarizing afterpotentials. These afterpotentials are classified into

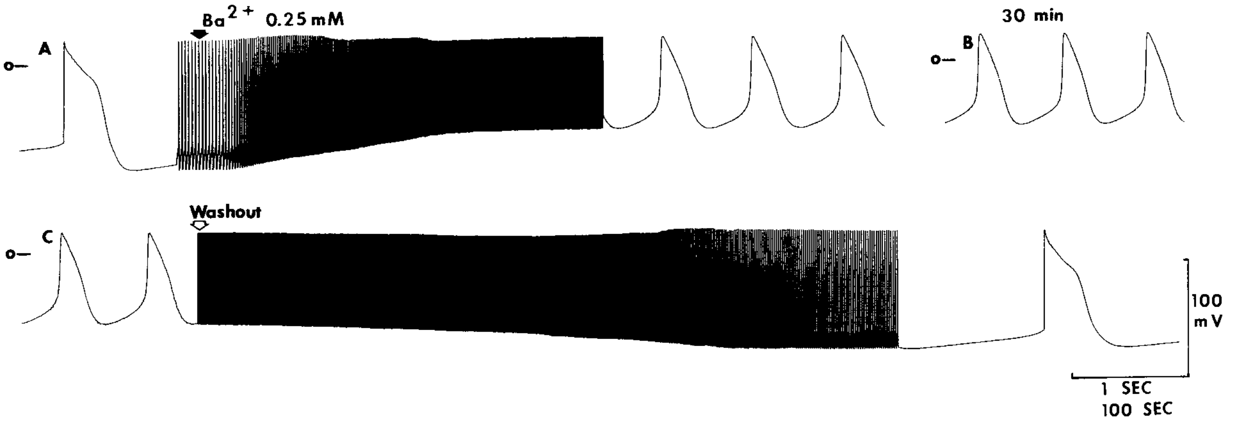


FIGURE 16–8

Induction of abnormal automaticity in a normal canine Purkinje fiber by superfusion with Tyrode's solution containing barium chloride, 0.25 mM. Exposure to barium (panel *A*) decreases maximal diastolic potential from about −90 mV to about −55 mV in 3 to 5 minutes. Rapid automaticity (abnormal automaticity) occurs. Abnormal automaticity is then sustained (panel *B*) until antiarrhythmic drugs are added or barium is washed out (panel *C*). This model of abnormal automaticity closely mimics naturally occurring forms in Purkinje fibers and myocardium damaged by ischemia or stretch. Traces were obtained from a pen recorder with limited frequency response and thus have attenuated spikes. Note the two different paper speeds: fast paper speed at the beginning and end of panels *A* and *C* and throughout *B*. Time and voltage calibrations are at lower right; zero reference potential is at left of each panel. (From Dangman KH, Miura DS. Electrophysiological effects of bethanidine sulfate on canine cardiac Purkinje fibers and ventricular muscle cells. J Cardiovasc Pharmacol 7:50, 1985, with permission.)

two subgroups: early afterdepolarizations and delayed afterdepolarizations.

EARLY AFTERDEPOLARIZATIONS. Early afterdepolarizations (EADs) occur during either phase 2 or phase 3 of the action potential. Triggered impulses occurring from maximum diastolic potentials of −60 to −20 mV can be generated from these early afterdepolarizations. These triggered impulses may occur as coupled single beats or as salvoes of extra beats (Fig. 16–9). In Purkinje fibers, triggered beats from early afterdepolarizations can occur after exposure to high concentrations of antiarrhythmic drugs (e.g., quinidine, *N*-acetylprocainamide, and cibenzoline), treatment with high concentrations of catecholamines, low oxygen tension, low pH (about 6.8), myocardial infarction, and exposure to toxic salts (i.e., barium chloride, cesium chloride) or organic toxins.[19–27]

In general, conditions that prolong action potential duration will tend to increase the amplitude of early afterdepolarizations and consequently the likelihood of triggering from the plateau level. Since action potential duration decreases when the rate of stimulation is increased, early afterdepolarizations generally are abolished by rapid drive.[19] Indeed, early afterdepolarizations may be transiently suppressed if a single beat is imposed at a shortened cycle length.[19] Likewise, if a toxic drug or salt is present, early afterdepolarizations may emerge if the dominant pacemaker rate is slowed.[19, 24]

Early afterdepolarizations may occur when the sodium window current is increased[25] and repolarizing (i_{K1}) current is decreased during phase 3,[28] or if sodium–calcium exchange is increased.[29] The triggered impulses from EADs are abolished by most agents or conditions that shorten action potential duration. Thus, increased extracellular potassium concentrations abolish EADs. Agents such as acetylcholine, lidocaine, and tetrodotoxin are also effective.[21, 22, 25, 28]

DELAYED AFTERDEPOLARIZATIONS. The second mechanism for triggered activity is the delayed afterdepolarization (DAD). DADs are afterdepolarizations occurring after full repolarization (Fig. 16–10). Triggered rhythms from DADs occur in isolated ventricular tissues following treatment with digitalis glycosides,[30–33] catecholamines,[34] and induction of myocardial infarction.[18, 35] Triggered activity from DADs can occur in coronary sinus tissues and mitral valve fibers.[36, 37]

In Purkinje fiber preparations treated with catecholamines or toxic doses of a cardiac glycoside (e.g., ouabain, 0.2 μM for 30 minutes), DADs can be elicited routinely. The amplitude and coupling interval of these DADs is directly proportional to the rate and duration of the train of action potentials that is used to elicit them. The amplitude of delayed afterdepolarizations and the incidence of triggered activity can be decreased by a variety of agents, including acetylcholine, slow inward current blocking compounds, local anesthetic drugs, and decreased calcium levels in the superfusate.

The ionic mechanisms for DADs have been studied

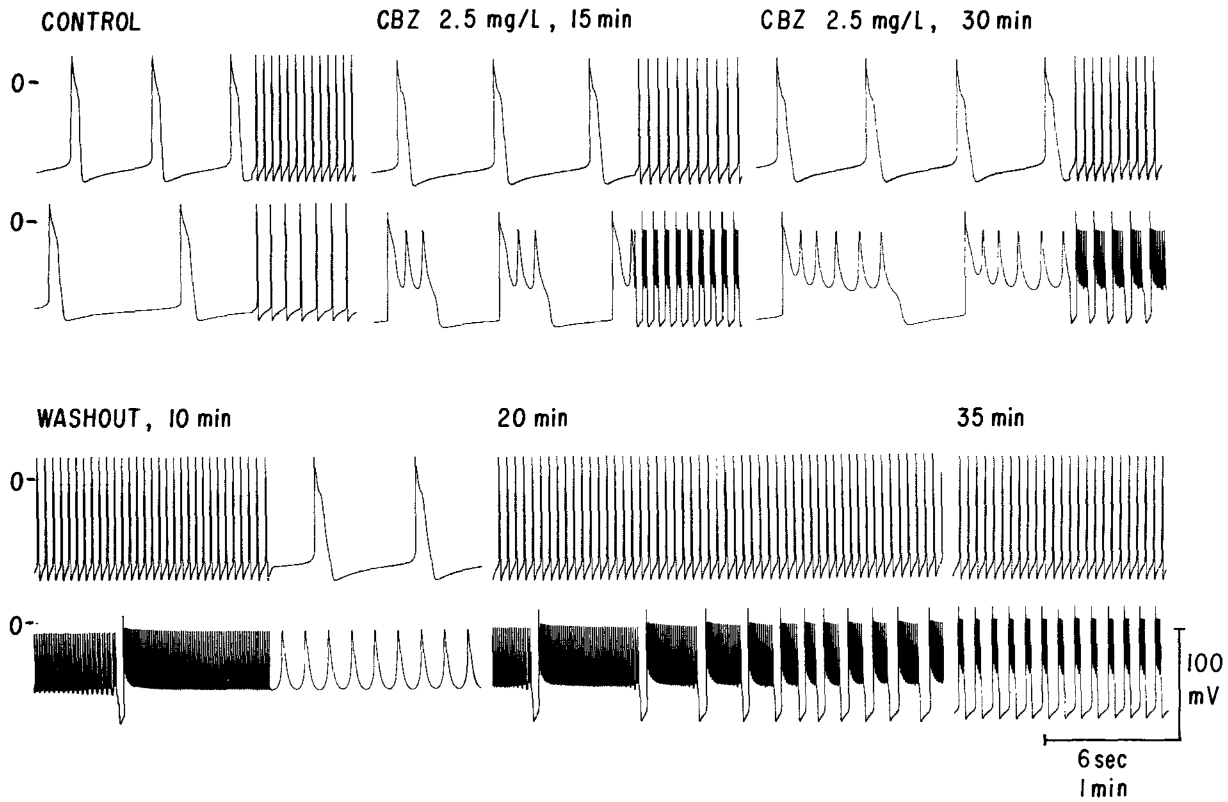


FIGURE 16–9

Early afterdepolarizations in Purkinje fiber treated with cibenzoline. Records show one impalement (as upper and lower traces in each panel) from each of two separate Purkinje fiber preparations from one heart. Development of drug effects is shown in the upper two panels at center and right, and "washout" of drug effects is shown in the lower two panels. Times are as indicated. Note that early afterdepolarizations occur in impalement in the lower trace, but not in the upper. During washout, long salvoes of triggered impulses (resembling abnormal automaticity) occur. The duration of these salvoes gradually shortened as washout was continued. The format for time and voltage calibration is as in Figure 16–8. (From Dangman KH. Cardiac effects of cibenzoline. J Cardiovasc Pharmacol 6:300, 1984; with permission.)

intensively, and it has been found that DADs occur when intracellular calcium ion activity is increased.[9, 13, 38, 39] This engenders a novel "transient inward" current (i_{TI}) that may result from either (1) the opening of nonspecific ion channels that carry sodium and potassium fluxes (i_{NaK}), or (2) inward currents created by electrogenic sodium–calcium ion exchange (i_{NaCa}).

ARRHYTHMIAS CAUSED BY ABNORMAL IMPULSE CONDUCTION

Two types of arrhythmias can be caused by abnormalities of impulse conduction: bradycardias can result from conduction blocks, and tachycardias (or single or multiple premature depolarizations) can result from re-entrant activation.

CONDUCTION BLOCKS

Simple conduction block can be diagnosed from surface electrocardiograms when failure of impulse propagation occurs at a critical point in the specialized conduction system. Such failures in conduction result in sinus node exit block, second- or third-degree atrioventricular block, and bundle branch or hemibranch block. Small areas of block within the working atrial or ventricular myocardium probably do not give rise to clinically significant changes in cardiac activation patterns (unless the block leads to the production of re-entrant activity as described later).

As mentioned earlier, conduction blocks can occur in myocardial tissues damaged by ischemia, infarction, stretch, or drug toxicity. Block of conduction through the atrioventricular node can also be produced by excessive vagal tone. Autoimmune diseases can lead to complete heart block in humans.[40, 41] For instance, congenital complete heart block can occur with neonatal lupus erythematosus.[40, 42] This condition is associated with high levels of antinuclear (anti-Ro/SS-A) antibodies and consequent inflammation and fibrosis in the cardiac conduction system. It is interesting that dogs can develop antinuclear antibodies,[43] and systemic lupus erythematosus (SLE) occurs in dogs and

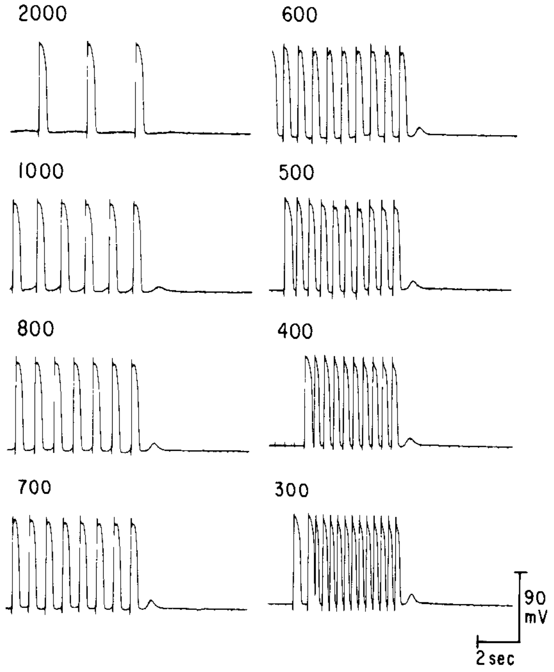


FIGURE 16–10

Delayed afterdepolarizations induced in a goat Purkinje fiber by treatment with isoproterenol, 1 uM. Each panel shows the effects of a stimulus train of 10 beats at cycle lengths between 2000 and 400 msec. The train shown at 300 msec did not conduct 1:1 and so consists of a total of 14 beats. Note that as the cycle length is decreased, the amplitude of the delayed afterdepolarization increases, and the coupling interval decreases. Voltage and time calibrations are shown at lower right. The maximum diastolic potential is approximately −94 mV throughout.

cats.[44] Also, it has been suggested that the pet dogs of patients with SLE develop antinuclear antibodies as a result of exposure to common environmental factors or transmissible agents.[44] Thus, some cases of heart block or myocarditis in dogs or cats may prove to be explained by autoimmune disease, although this remains to be verified.

RE-ENTRANT ACTIVATION

In normal sinus rhythm, the atria and ventricles are activated in a specific, efficient, and relatively constant pattern. Each normal cardiac impulse dies as the wavefront reaches the limits of the cardiac syncytium in the ventricular subepicardium. The myocardium is then activated again only after it is invaded by the next normal sinus impulse (see Fig. 16–2). If re-entrant activation occurs, the propagating impulse does not die out in the usual way; rather, it persists to re-excite the chambers of the heart after the end of the refractory period. Thus, re-entry can produce premature beats; either the atria or the ventricles can be involved in the re-entrant activity.

In both canine and feline hearts, the refractory period of the atrium is approximately 150 msec, and the refractory period of the ventricular tissues is usually from 200 to 500 msec. Therefore, an impulse that is capable of causing re-entry in hearts of these species must be sequestered in a zone of cardiac tissue for an appreciable time so it can emerge and re-excite the heart at the end of the refractory period.

In re-entry, the impulse does not remain stationary while awaiting the end of the refractory period. Instead, the impulse must continue to conduct slowly through a pathway that is functionally or anatomically isolated from the rest of the myocardial syncytium. This isolated conduction pathway, which generally will be composed of a very small percentage of the heart, must provide a route by which the impulse can return to the normal regions of the heart that have previously been excited. The pathway also must be sufficiently long to allow enough time for the impulse to continue to propagate until the end of the absolute refractory period.

The cardiac impulse propagates very quickly (1 to 5 meters per second) in normal atrial and ventricular myocardial fibers. This means that if re-entry were to occur in the normal myocardium, the length of the electrically isolated pathway needed for the sequestration of the impulse would be very long (e.g., at least 150 cm in the atrium and at least 200 to 500 cm in the ventricle. Electrically isolated pathways of this length are not likely to exist in the normal heart. In diseased hearts, however, conduction velocities can be very slow. Therefore, the necessary pathway length for the isolated segment of a re-entrant circuit could be very short.[11]

In summary, the necessary conditions for development of re-entry are the occurrence of (1) unidirectional conduction block, and (2) slow conduction (relative to refractoriness of the surrounding cardiac cells). In the normal heart, the tissues that are the most likely anatomic substrates for re-entry are those of the sinus and atrioventricular nodes. This is because, as discussed later, the nodal tissues have relatively poorly coupled cells, generate slow response action potentials, and show time-dependent refractoriness. This may allow parallel conduction pathways with "functional longitudinal dissociation" to occur, and these parallel dissociated pathways may support re-entry.

In contrast to nodal tissues, the working atrial and ventricular myocardial tissues will support slow conduction and unidirectional conduction block only if significant pathology is present. Such re-entrant arrhythmias in the myocardium are generally considered to be of greater clinical significance than are nodal arrhythmias. That is, life-threatening re-entrant arrhythmias are far more likely to occur in the diseased heart than in the normal heart. There are two basic types of change in cellular electrophysiology of cardiac cells

that can predispose to the development of slow conduction and unidirectional conduction block: (1) decreased maximum diastolic potential, and (2) increased dispersion of refractoriness.

RE-ENTRY DEPENDENT ON SLOW CONDUCTION AND UNIDIRECTIONAL CONDUCTION BLOCK IN PARTIALLY DEPOLARIZED TISSUE WITH DEPRESSED ACTION POTENTIALS. This type of re-entry can depend on an anatomic loop of tissue, composed of atrial, ventricular, or Purkinje fibers, with appropriate electrophysiologic characteristics. This is classic re-entry.[45–48]

In the mammalian heart, the anatomy of the ventricular conduction system is such that after ischemic damage or stretch, pathways can occur that are functionally suitable for re-entry. The Purkinje system originates in the His bundle; it then divides into the left and right bundle branches. Each of these bundle branches then divides again and again over most of the endocardial surface of both ventricles. Each of the major bundles of Purkinje fibers is invested with a covering layer of connective tissue. This tends to keep each bundle electrically isolated from the underlying ventricular muscle as well as from the other strands of Purkinje tissue running in parallel to it. In the His bundle and bundle branches, the strands of fibers usually anastomose quite freely. More peripherally, the terminal Purkinje fibers arborize many times and contact endocardial ventricular muscle cells (Fig. 16–11). These ventricular muscle cells are connected syncytially.

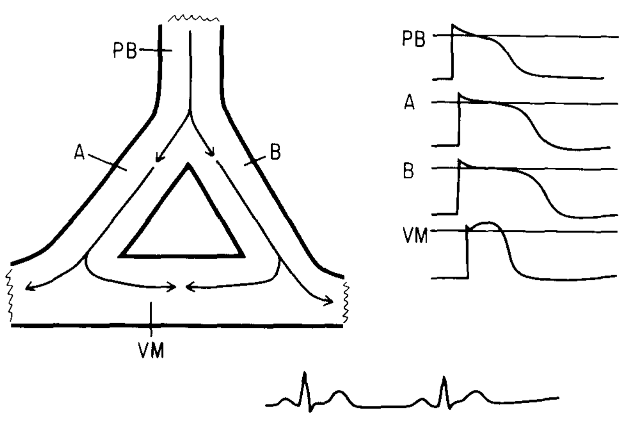


FIGURE 16–11

Illustration of normal conduction of the cardiac impulse in the ventricular conduction system. The Schmitt/Erlanger diagram[48] at left shows one of the bifurcations of the His-Purkinje system; PB denotes proximal bundle, A and B denote distal branches, VM denotes ventricular muscle distal to branches. Action potential duration and refractory periods are longest in the "gate" regions of distal branches A and B. The impulse normally conducts down through each branch and simultaneously activates the endocardial ventricular muscle in contact with the ultimate transitional fibers of each branch. The wavefronts of activation then collide in the ventricular muscle zone and terminate. Action potentials at right are from points indicated in the drawing at left; action potentials indicate the activation sequence in the ventricle, producing an electrocardiogram of normal sinus rhythm as shown below.

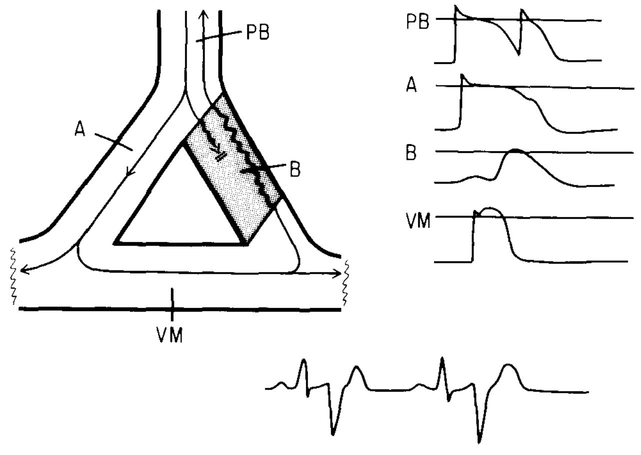


FIGURE 16–12

Re-entry in the Schmitt/Erlanger diagram.[48] The impulse propagates through the proximal bundle (PB) and distal bundle A in the normal manner. Distal bundle B is damaged: the antegrade impulse conducts slowly and decrementally through B (wavy line) and blocks in the damaged zone. The impulse conducts through the ventricle and re-enters the damaged zone from the distal margin. The impulse propagates back to the proximal bundle and re-enters the proximal bundle, where it continues to be conducted in the retrograde direction. This can give rise to a premature ventricular depolarization (displayed on the electrocardiogram below). If every primary (sinus) impulse is followed by a premature depolarization, this can produce a bigeminal rhythm.

Therefore, junctional sites between Purkinje fibers and muscle can form anatomic loops. Normally, the cardiac impulse quickly propagates through all branches of the ventricular conduction system to the subendocardial ventricular muscle. Normal impulses are terminated in ventricular muscle when the advancing wavefronts collide and are surrounded by refractory tissue (see Fig. 16–11).

Re-entry can occur in the distal Purkinje network if conduction velocity is decreased and unidirectional block occurs at a critical site (Fig. 16–12). Obviously, if a zone of damage encompasses one or more of these Purkinje fiber–ventricular muscle loops, diastolic potential, action potential amplitude, and upstroke velocity may be reduced in the damaged fibers. Slow conduction and unidirectional block may occur. Since the intensity of insult in the damaged zone rarely is uniform, some areas within the loop will be more depressed than others. Unidirectional conduction block will usually occur in one of the areas of greatest depression. If, however, depression of the action potentials is too great, no conduction will be supported, and bidirectional conduction block will result. Under these circumstances, re-entry will not occur. Because the degree of depression is critical for the development of unidirectional conduction block, and this can vary from site to site in a zone of damage, re-entry is more likely to occur in a large zone of damage than a small one. Once a re-entrant circuit is established, it may support either single premature impulses or multiple

premature responses (i.e., a tachycardia). Re-entrant tachycardias resulting from continuous circling of the impulse around the loop are called *circus movement* tachycardias.

In some cases, the zone of damage may not have appropriate electrophysiologic characteristics (i.e., severely enough depressed action potentials) to precipitate re-entry at normal (sinus rhythm) cycle lengths. In these cases, re-entry may be provoked by premature impulses, which may originate from either supraventricular or ventricular foci. The premature impulses are more likely to precipitate re-entry because Purkinje fibers in a zone of damage will usually have a much longer refractory period than fibers in normal zones. If the depressed Purkinje fibers are activated prematurely, the premature impulse will be conducted more slowly and have a greater tendency to block than will an impulse elicited at the longer (normal) cycle length. In other words, premature impulses often can lead to re-entrant responses because at short cycle lengths there is a reduced "safety factor" for conduction in the myocardium.

Sites of re-entry over fixed anatomic pathways are not exclusively found in the peripheral Purkinje system. It is likely that similar re-entry loops could involve the His bundle and bundle branches, or major proximal fascicles of the conduction system. In these cases, re-entry might occur as a result of bundle branch blocks or hemiblocks, respectively. Re-entry loops can also be formed in pathologic zones of working atrial or ventricular muscle. For example, cardiomyopathy can produce areas of inexcitable atrial tissue, which can create pathways for circus movement. Finally, the existence of an anatomically discrete loop is not an absolute requirement for the development of slow conduction, unidirectional conduction block, and re-entry. Re-entry can occur in unbranched bundles of fibers or sheets of tissue if "functional longitudinal dissociation" occurs and is accompanied by slow conduction and unidirectional conduction block.

RE-ENTRY DEPENDENT ON DISPERSION OF REFRACTORINESS. Recently, it has been demonstrated that re-entry can occur not only in depressed, depolarized tissues, but also in cardiac tissues in which the cells have normal diastolic potentials and rapid rates of depolarization. However, the same two basic electrophysiologic phenomena must be present to support re-entrant activation in these fully polarized tissues: that is, the preparation must still support unidirectional conduction block and slow conduction. Although undamaged tissues probably will not show slow conduction and unidirectional conduction block at normal sinus rates, both conduction abnormalities may occur during propagation of premature impulses through relatively refractory cardiac tissues.

Re-entry occurring as a result of dispersion of refractoriness was described in isolated rabbit left atrium.[49–51] In this "leading circle" model, re-entry occurs in the absence of an anatomic obstacle. The initiation of re-entrant activity is permitted when atrial fibers in close proximity to each other have different refractory periods. Re-entry can be initiated when a premature impulse fails to conduct through fibers with long refractory periods and conducts through fibers with shorter refractory periods. Eventually, the impulse returns to the initial site of unidirectional block in the retrograde direction after excitability recovers there. The impulse may then persist in a circus movement over an anatomically variable circuit with a perimeter of as little as 6 to 8 mm. The conduction velocity within the circuit is relatively slow because the impulses are propagating through partially refractory tissues. Impulses spread inward from the perimeter continuously, leading to a central zone of the re-entrant circuit that is functionally inactive. The amplitudes of the action potentials, and their maximum upstroke velocities, decrease gradually from the periphery to the center of the circuit. Cells in the center of the re-entrant circuit produce only local responses rather than full action potentials dependent on regenerative responses. This is because they are continuously kept in a partially depolarized and refractory state by the circulation of the impulse about them. The length of the circuit and the circulation time of the loop are controlled by the conduction velocity and refractory period of the fibers composing it.

A second example of re-entry dependent on dispersion of refractoriness occurs in the atrioventricular (AV) node preparation. As mentioned earlier, in AV node cells, the time needed for full recovery of excitability does not begin at the end of phase 3 but instead lasts well into phase 4. That is, these cells show time-dependent refractoriness rather than voltage-dependent refractoriness.[52] Re-entry can occur in this preparation because adjacent zones of the node are functionally different electrophysiologically. The recovery period can be different in the two zones of the node, and if these differences are significant enough, re-entry can occur following a premature impulse. This is because, following a premature impulse, the differences in the refractory periods of the two populations of AV nodal cells functionally divide the node into two pathways. If conduction of the premature impulse through the node is slow enough, it may return to the atrium as a *return extrasystole.* If this return extrasystole propagates through the atrium at a time when the antegrade approaches to the node have recovered excitability, the impulse may again enter the AV node and conduct around the circuit. This can become a continuous process and may lead to paroxysmal supraventricular tachycardias with some degree of AV block.

Differences in refractoriness can also lead to re-entry in the ventricle. However, as in the examples cited in

the atrium and the AV node, an appropriately timed premature impulse is needed to elicit this re-entrant activity. An example of re-entrant activation of the ventricles dependent on differences in refractoriness is the *R-on-T phenomenon,* in which ventricular fibrillation is produced by premature impulses elicited during the peak of the T wave. Local differences in refractoriness can be accentuated by cardiac disease, producing a predisposition to R-on-T re-entry.

ARRHYTHMIAS CAUSED BY SIMULTANEOUS DERANGEMENTS OF IMPULSE INITIATION AND IMPULSE CONDUCTION

It is probable that many of the arrhythmias occurring clinically are not caused by a single electrophysiologic mechanism but represent two or more mechanisms operating simultaneously. Perhaps the simplest example of these multifactorial arrhythmias is *parasystole.* Here, premature depolarizations (in either the atria or the ventricles) occur infrequently and are randomly distributed during diastole. Intervals between these ectopic impulses are whole number multiples of one basic cycle length that is presumed to be the cycle length of an ectopic pacemaker. That is, parasystole is thought to reflect the activity of an independent ectopic pacemaker that is protected from sinus node overdrive by a complete entrance block, and the ectopic impulses are thought to reflect the escape of this ectopic impulse through a zone of variable exit block.

Another example of an arrhythmia caused by more than one mechanism occurring simultaneously is found in the multifocal ventricular arrhythmias in the digitalis-intoxicated dog or cat. These arrhythmias may result from enhanced normal automaticity, delayed afterdepolarization-induced triggered activity, and re-entrant activity.

SUMMARY AND CLINICAL CONSIDERATIONS

This chapter has reviewed the electrophysiologic mechanisms of cardiac arrhythmias. Bradyarrhythmias can be caused by excessive vagal tone (e.g., sinus bradycardia) or atrioventricular blocks. Tachyarrhythmias can be caused by enhanced automaticity, triggered activity, or re-entrant activation. These cellular arrhythmic mechanisms may be induced by more basic electropathophysiologic changes that can result from ischemic or toxic damage to the ventricular or atrial myocardium. Decreases in diastolic membrane potential can promote (1) enhanced ectopic or abnormal automaticity, (2) triggered activity from delayed afterdepolarizations, and (3) conduction blocks and/or re-entrant activity. The effects of decreases in diastolic potential on impulse conduction are often mediated by decreases in the rate of rise and amplitude of phase 0 of the action potentials. In addition, alterations in action potential duration and refractoriness may occur in stretched, ischemic, infarcted, or scarred myocardium, with or without great changes in diastolic membrane potential, and these changes may lead to conduction blocks or re-entrant activity.

Direct applications of the cellular electrophysiology of cardiac arrhythmias to the clinical setting is still limited. In part this is because almost all studies of cardiac pathophysiology and the cellular mechanisms of arrhythmias have been carried out in experimental animal models. The more common models for study of ventricular arrhythmias include digitalis toxicity and coronary artery ligation.[53-55] For atrial tachycardias, they include "anatomic barrier" models and tricuspid insufficiency.[56-59] As reviewed earlier, ventricular arrhythmias from digitalis intoxication are caused by triggered activity from delayed afterdepolarizations, enhanced automaticity, or re-entry. Multifocal arrhythmias in acute myocardial infarctions occurring 10 to 30 hours after onset of ischemia in the canine heart are largely attributed to abnormal automaticity or triggered activity. Arrhythmias in hearts with older, more organized myocardial infarcts are caused by re-entrant excitation, as are most forms of experimental atrial arrhythmias.

However, experimental models may not perfectly mimic the intended clinical situations, and good models are not available for many types of cardiac pathophysiology. For instance, very limited information is available on cellular mechanisms of arrhythmias in heart failure, and the few studies of the electrophysiology of cardiomyopathy have provided conflicting results.[60] For the most part, we can only extrapolate data from more general models of arrhythmia.

In recent years, research on the causes and therapy of arrhythmias has expanded to involve two new approaches. Electrophysiologists have shifted their interest to the molecular biology of ion channels. The goal of this work is to understand the fundamentals of ion channel function.[1] One then may be able to explain how derangements of these channels' function can lead to abnormalities of impulse initiation or conduction. Simultaneously, scientific interest has also been focused on the role of chemical mediators in ventricular arrhythmias.[61] It has long been known that alterations of potassium levels, elevated catecholamines, or histamine can cause arrhythmias. Moreover, a contributing role has been suggested for amphophils, arachidonic acid metabolites (prostaglandins, leukotrienes, and thromboxane), angiotensin II, free radicals, and

endothelin in arrhythmias. Exactly how these chemical agents produce arrhythmias generally remains to be explained.

REFERENCES

1. Tomaselli GF, Backx PH, Marban E. Molecular basis of permeation in voltage gated ion channels. Circ Res 72:491, 1993
2. Campbell DL, Rasmusson RL, Strauss HC. Electrophysiology of the sinus node: Ionic and cellular mechanisms underlying primary cardiac pacemaker activity. *In* Dangman KH, Miura DS (eds): Electrophysiology and Pharmacology of the Heart: A Clinical Guide. New York, Marcel Dekker, 1991, p 59
3. Dangman KH. Electrophysiology of the Purkinje fiber. *In* Dangman KH, Miura DS (eds): Electrophysiology and Pharmacology of the Heart: A Clinical Guide. New York, Marcel Dekker, 1991, p 161
4. Noble D. The Initiation of the Heartbeat. Oxford, Clarendon Press, 1975
5. Allen JD, Brennan FJ, Wit AL. Actions of lidocaine on transmembrane potentials of subendocardial Purkinje fibers surviving in infarcted canine hearts. Circ Res 43:470, 1978
6. Dangman KH. Effects of bepridil on transmembrane action potentials recorded from canine cardiac Purkinje fibers and ventricular muscle cells; Insights into antiarrhythmic mechanisms. Naunyn Schmiedebergs Arch Pharmacol 329:326, 1985
7. Dangman KH. Effects of procainamide on automatic and triggered impulse initiation in isolated preparations of canine cardiac Purkinje fibers. J Cardiovasc Pharmacol 12:78, 1988
8. Cranefield PF. The conduction of the cardiac impulse: The slow response and cardiac arrhythmias. Mount Kisco, NY, Futura Publications, 1975
9. Noble D. The surprising heart: A review of recent progress in cardiac electrophysiology. J Physiol 353:1, 1984
10. Hoffman BF, Rosen MR. Cellular mechanisms for cardiac arrhythmias. Circ Res 49:1, 1981
11. Wit AL, Cranefield PF. Reentrant excitation as a cause of cardiac arrhythmias. Am J Physiol 235:H1, 1978
12. Hoffman BF, Dangman KH. Demonstration of the mechanisms for arrhythmias in experimental animals. Ann NY Acad Sci 432:17, 1984
13. DiFrancesco D, Noble D. A model of cardiac electrical activity incorporating ionic pumps and concentration changes. Phil Trans Soc Lond (Ser B) 307:353, 1985
14. Vassalle M, Kotake H, Lin CI. Pacemaker current, membrane resistance, and K^+ in sheep cardiac Purkinje fibers. Cardiovasc Res 26:383, 1992
15. LeMarec H, Dangman KH, Danilo P, Rosen MR. An evaluation of automaticity and triggered activity in the canine heart one to four days after myocardial infarction. Circulation 71:1224, 1985
16. Hiraoka M, Ikeda K, Sano T. The mechanism of Ba-induced automaticity in ventricular muscle fibers. J Mol Cell Cardiol 10(Suppl I):35, 1978
17. Opie LH. The Heart. Physiology, Metabolism, Pharmacology and Therapy. London, Grune and Stratton, 1984
18. Dangman KH, Hoffman BF. Effects of nifedipine on electrical activity of cardiac cells. Am J Cardiol 46:1059, 1980
19. Dangman KH, Hoffman BF. *In vivo* and *in vitro* antiarrhythmic and arrhythmogenic effects of *N*-acetyl procainamide. J Pharmacol Exp Ther 217:851, 1981
20. Dangman KH. Cardiac effects of cibenzoline. J Cardiovasc Pharmacol 6:300, 1984
21. Roden DM, Hoffman BF. Action potential prolongation and induction of abnormal automaticity by low quinidine concentrations in canine Purkinje fibers. Relationship to potassium and cycle length. Circ Res 56:857, 1985
22. Coraboeuf E, Deroubaix E, Coulombe A. Acidosis-induced abnormal repolarization and repetitive activity in isolated dog Purkinje fibers. J Physiol (Paris) 76:97, 1980
23. Hoffman BF, Cranefield PF. Electrophysiology of the Heart. New York, McGraw-Hill, 1960
24. Brachmann J, Scherlag BJ, Rosenstraukh LV, Lazzara R. Bradycardia-dependent triggered activity: Relevance to drug-induced multiform ventricular tachycardia. Circulation 68:846, 1983
25. Brown BS. Early afterdepolarizations induced by batrachytoxin: Possible involvement of sodium current. Fed Proc 42:581, 1983
26. Trautwein W. Generation and conduction of impulses in the heart as affected by drugs. Pharmacol Rev 15:277, 1963
27. Dangman KH, Hoffman BF. Effects of single premature stimuli on automatic and triggered rhythms in isolated canine Purkinje fibers. Circulation 71:813, 1985
28. Coraboeuf E. Role of ionic currents in the genesis of normal and abnormal automatisms in cardiac tissues. *In* Antaloczy Z, Preda I (eds): Proceedings, 8th International Congress on Electrocardiology, 1981. Amsterdam, Excerpta Medica, 1982, p 1
29. Fischmeister R, Vassort G. The electrogenic Na-Ca exchange and cardiac electrical activity. I. Stimulation of Purkinje fibre action potential. J Physiol (Paris) 77:705, 1981
30. Rosen MR, Gelband H, Hoffman BF. Correlation between effects of ouabain on the canine electrocardiogram and transmembrane potentials of isolated Purkinje fibers. Circulation 47:65, 1973
31. Rosen MR, Gelband H, Merker C, Hoffman BF. Mechanisms of digitalis toxicity. Effects of ouabain on phase 4 of canine Purkinje fiber transmembrane potentials. Circulation 47:681, 1973
32. Ferrier GR, Moe GK. Effect of calcium on acetylstrophanthidin-induced transient depolarization in canine Purkinje tissue. Circ Res 33:508, 1973
33. Karaguezian HS, Katzung BG. Voltage clamp studies of transient inward current and mechanical oscillations induced by ouabain in ferret papillary muscle. J Physiol 327:255, 1982
34. Dangman KH, Danilo P, Hordof AJ, et al. Electrophysiologic characteristics of human ventricular and Purkinje fibers. Circulation 65:362, 1982
35. El Sherif N, Gough WB, Zeiler RH, Mehra R. Triggered ventricular rhythms in 1-day-old myocardial infarction in the dog. Circ Res 52:566, 1983
36. Wit AL, Cranefield PF. Triggered and automatic activity in the canine coronary sinus. Circ Res 41:435, 1977
37. Wit AL, Cranefield PF. Triggered activity in cardiac muscle fibers of the simian mitral valve. Circ Res 38:85, 1976
38. Kass RS, Lederer WJ, Tsien RW, Weingart R. Role of calcium ions in transient inward current and aftercontractions induced by strophanthidin in cardiac Purkinje fibres. J Physiol 281:187, 1978
39. Brown HF, Noble D, Noble SJ, Taupignon AI. Relationship between the transient inward current and slow inward currents in the sino-atrial node of the rabbit. J Physiol 370:299, 1986

40. Olah KS, Gee H. Fetal heart block associated with maternal anti-Ro (SS-A) antibody—current management: A review. Br J Obstet Gynaecol 98:751, 1991
41. Yokoi K, Akaike M, Nishiuchi T, et al. Scar formation in the cardiac conduction system of a patient with Takayasu's arteritis. Cardiology 81:378, 1992
42. Alexander E, Buyon JP, Provost TT, Guarnieri T. Anti-Ro/SS-A antibodies in the pathophysiology of congenital heart block in neonatal lupus syndrome, an experimental model. In vitro electrophysiologic and immunocytochemical studies. Arthritis Rheum 35:176, 1992
43. White SD, Posychuk RAW, Schur PH. Investigation of antibodies to extractable nuclear antigens in dogs. Am J Vet Res 53:1019, 1992
44. Jones DRE, Hopkinson ND, Powell RJ. Autoantibodies in pet dogs owned by patients with systemic lupus erythematosus. Lancet 339:1378, 1992
45. Mayer AG. Rhythmical Pulsation in Scyphomedusae. Washington, DC, Carnegie Institute, Pub 47, 1906, p 1
46. Mines GR. On dynamic equilibrium in the heart. J Physiol 46:349, 1913
47. Mines GR. On circulating excitations in heart muscles and their possible relation to tachycardia and fibrillation. Trans R Soc Can, Ser 3, Sect IV, 8:43, 1914
48. Schmitt FO, Erlanger J. Directional differences in the conduction of the impulse through heart muscle and their possible relation to extrasystolic and fibrillary contractions. Am J Physiol 87:326, 1928
49. Allessie MA, Bonke FIM, Schopman FJG. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. Circ Res 33:54, 1973
50. Allessie MA, Bonke FIM, Schopman FJG. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. II. Role of nonuniform recovery of excitability in the occurrence of unidirectional block, as studied with multiple microelectrodes. Circ Res 39:168, 1976
51. Allessie MA, Bonke FIM, Schopman FJG. Circus movement in rabbit atrial tissue as a mechanism of tachycardia. III. The "leading circle" concept: A new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ Res 41:9, 1977
52. Mendez C, Moe GK. Some characteristics of transmembrane potentials of AV nodal cells during propagation of premature beats. Circ Res 19:993, 1966
53. Ferrier GR. Digitalis toxicity. *In* Dangman KH, Miura DS (eds): Electrophysiology and Pharmacology of the Heart: A Clinical Guide. New York, Marcel Dekker, 1991, p 277
54. Patterson E, Scherlag BJ, Lazzara R. Arrhythmias in the canine heart two to twenty-four hours after myocardial infarction. *In* Dangman KH, Miura DS (eds): Electrophysiology and Pharmacology of the Heart: A Clinical Guide. New York, Marcel Dekker, 1991, p 301
55. El-Sherif N, Restivo M, Gough WB. Reentrant ventricular rhythms in the three-to-five-day-old canine postinfarction heart. *In* Dangman KH, Miura DS (eds): Electrophysiology and Pharmacology of the Heart: A Clinical Guide. New York, Marcel Dekker, 1991, p 331
56. Frame LH, Page RL, Hoffman BF. Atrial reentry around an anatomic barrier with a partially excitable gap: A canine model of flutter. Circ Res 58:495, 1986
57. Boyden PA. Reentrant excitation in the atrium. *In* Dangman KH, Miura DS (eds): Electrophysiology and Pharmacology of the Heart: A Clinical Guide. New York, Marcel Dekker, 1991, p 239
58. Boyden PA, Hoffman BF. The effects on atrial electrophysiology and structure of surgically induced right atrial enlargement in dogs. Circ Res 49:1319, 1981
59. Boyden PA. Activation sequence during atrial flutter in dogs with surgically induced right atrial enlargement. Circ Res 62:596, 1988
60. Pye MP, Cobbe SM. Mechanisms of ventricular arrhythmias in cardiac failure and hypertrophy. Cardiovasc Res 26:740, 1992
61. Curtis MJ, Pugsley MK, Walker MJA. Endogenous chemical mediators of ventricular arrhythmias in ischaemic heart disease. Cardiovasc Res 27:703, 1993

17

Pharmacology and Pharmacokinetics of Antiarrhythmic Drugs

WILLIAM W. MUIR, III
RICHARD A. SAMS
N. SYDNEY MOÏSE

ANTIARRHYTHMIC DRUG CLASSIFICATION SCHEMES

The spectrum of drugs with potential utility for treating disturbances in cardiac rhythm continues to grow. Clinical efficacy depends in part on the factors causing the arrhythmia (Table 17–1). Given that all cardiac arrhythmias are linked to one or more cellular electrophysiologic abnormalities,[1-8] schemes to classify mechanisms of arrhythmogenesis (chapter 16) and antiarrhythmic drugs have been developed based upon each drug's principal electrophysiologic properties.[9-12] The most popular of these schemes was developed by Vaughan-Williams with modifications by Harrison. It classifies drugs according to their predominant electrophysiologic action (Table 17–2)[9-13] based upon their ability to block trans-sarcolemmal flux of sodium (Class I) or calcium (Class IV) ions; antagonize the sympathetic nervous system (Class II); and prolong the duration of the cardiac action potential, thereby increasing cardiac refractoriness (Class III).

Regardless of this classification scheme's ability to aid in categorizing drugs, its clinical usefulness in determining which drug to select to treat a specific cardiac arrhythmia remains questionable.[14, 15] This is due to the fact that arrhythmias are frequently caused by several mechanisms (see Table 16–1), and that the classes of antiarrhythmic drugs produce electrophysiologic effects that frequently overlap. For example, amiodarone not only increases refractoriness but blocks trans-sarcolemmal sodium flux and possesses β-adrenergic-blocking activity (Tables 17–2 and 17–3). Ideally, a drug classification scheme based on the mechanisms for cardiac arrhythmias would be more useful. This approach is just beginning to be appreciated for its clinical relevance (chapter 18). It has been based on known cellular mechanisms for cardiac arrhythmias ("vulnerable parameter") and the use of drugs that are most likely to modulate the vulnerable parameter therapeutically (Tables 17–4, 17–5; see also chapter 16).[14, 15]

THE VAUGHAN-WILLIAMS CLASSIFICATION

CLASS I

Class I antiarrhythmic drugs are referred to as membrane stabilizers and produce their principal electrophysiologic effects by depressing transmembrane sodium flux and phase 0 of the cardiac action potential. Many of the drugs within this class are local anesthetics. Class I antiarrhythmic drugs have been subdivided into three subgroups (Ia, Ib, Ic) based upon their ability to slow conduction velocity and alter action potential duration (see Table 17–2). Class Ia drugs (which include quinidine, procainamide, and disopyramide) depress phase 0 of the action potential, depress conduction velocity, prolong action potential duration, and delay repolarization. Lidocaine, mexiletine, tocainide, and phenytoin (Class Ib) produce little to no effect on phase 0 of the action potential or conduction velocity in normal heart tissue but depress phase 0 and decrease conduction velocity in diseased tissues. Drugs in Class Ib also shorten action potential duration and increase ventricular fibrillation threshold. Class Ic drugs (e.g., propafenone) cause marked depression of phase 0 of the action potential and conduction velocity but produce minimal effects on repolarization and refractoriness (see Table 17–2).

CLASS II

Class II antiarrhythmic drugs produce antisympathetic or sympatholytic effects (see Table 17–2). Although many antiarrhythmic drugs are noted for their effects on autonomic tone (see Table 17–3), Class II drugs include the β-adrenoceptor-blocking drugs and drugs with both α- and β-adrenoceptor-blocking activity (e.g., labetalol). This class of drugs produces their principal antiarrhythmic effects by blocking β_1-adrenoceptors. Because α_1-adrenoceptor stimulation may be an important cause of spontaneously occurring arrhythmias induced by ischemia and drugs such as thiobarbiturates and halothane which "sensitize" the heart, the clinical use of mixed α- and β-adrenoceptor-blocking drugs has been proposed as more effective than β-blocking drugs alone.[16] Clinically, the potentially beneficial effects of adrenoceptor-blocking drugs are dependent on the prevailing autonomic tone, particularly sympathetic tone.[17] Larger drug dosages are required when sympathetic tone is high. Quinidine-like or membrane-stabilizing properties are frequently ascribed to many of the β-adrenoceptor-blocking drugs but are unlikely to play a significant role in producing clinically relevant antiarrhythmic effects because these effects are appreciated only at doses larger than those that produce β-adrenergic blockade. Similarly, β_1-cardioselectivity, intrinsic sympathomimetic activity, and potency ratio do not appear to contribute to the effectiveness of this class of drugs (see Table 17–3).[18]

TABLE 17–1
Common Clinical Causes of Cardiac Arrhythmias

Central nervous system disease or trauma
Peripheral or reflex-mediated alterations in neural tone
Infections (viral or bacterial)
Trauma
Degenerative or fibrotic conditions
Congenital or acquired heart disease
Neurohumoral and endocrine influences
Acid-base and electrolyte disturbances
Hypoxia, hypercapnia, and temperature changes
Autonomic imbalance
Ischemia
Toxic substances and drugs

Modified from Muir WW III, Sams RA. Pharmacology and pharmacokinetics of antiarrhythmic drugs. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 309.

CLASS III

Class III antiarrhythmic drugs prolong action potential duration and refractoriness without significantly depressing the rate of phase 0 or conduction velocity (see Table 17–2). Some Class III drugs may possess sodium channel (Class I)-blocking effects but are recognized more for their antifibrillatory activity.[19–23] Although Class III antiarrhythmic drugs have been extensively studied and advocated in human patients, their use in veterinary medicine is just beginning and their effectiveness has yet to be determined.

CLASS IV

Class IV antiarrhythmic drugs inhibit the entry of calcium ions into cells and are collectively referred to as calcium channel-blocking drugs (see Table 17–2). These drugs block the slow inward calcium current ($I_{Ca\text{-}L}$). Calcium plays a pivotal role in regulating both the electrical and mechanical activity of cardiac and vascular tissues.[24–32] The selectivity of a calcium channel blocker for cardiac or vascular tissue depends on the specific binding site to the calcium channel.[23, 31, 32] The dihydropyridines (nifedipine, amlodipine) are selective for the vascular smooth muscle. Therefore, these drugs are used to treat systemic hypertension. In contrast, the prototype calcium channel blockers diltiazem and verapamil, each of which binds to a different site on the calcium channel, are cardioselective. Although diltiazem is used to treat systemic hypertension, its effects on vascular smooth muscle are less potent than those of amlodipine, and it more readily causes sinus bradycardia and slowed atrioventricular (AV) nodal conduction. Electrophysiologically, calcium is particularly important in maintaining normal automaticity and conduction within the sinoatrial (SA) and AV nodes. Antiarrhythmic activity (supraventricular ar-

TABLE 17–2
Classification of Antiarrhythmic Drugs

Drug Class		Basis for Classification	Predominant Electrophysiologic Effects
Class I		Class I drugs are generally considered membrane stabilizers; most are noted for their ability to block Na^+ channels	
Ia	Quinidine Procainamide Disopyramide Acecainide* Pirmenol*		Depress phase 0 Slow conduction velocity Prolong repolarization
Ib	Lidocaine Tocainide Mexiletine Moricizine Phenytoin		Depress phase 0 in abnormal tissue Shorten repolarization
Ic†	Propafenone Lorcainide Indecainide Cibenzoline		Depress phase 0 Markedly slow conduction velocity
Class II	Propranolol Nadolol Atenolol Metoprolol Esmolol Labetalol	Class II drugs are sympatholytic and are noted for their ability to block β_1- and α_1-adrenoceptors	Depress phase 4 Prolong repolarization Minimally slow conduction velocity
Class III‡	Amiodarone Bretylium Sotalol Clofilium* Sematilide*	Class III drugs prolong the action potential duration and effective refractory period	Depress phase 4 in the sinus and atrioventricular nodes Prolong conduction time through the sinus and atrioventricular nodes
Class IV	Verapamil Diltiazem Gallopamil*	Class IV drugs block calcium channels, particularly $I_{Ca\text{-}L}$	Depress phase 4 in the sinus and atrioventricular nodes Prolong conduction time through the sinus and atrioventricular nodes
Class V§	Alinidine	Class V drugs block anionic (Cl^-) channels; these drugs produce bradycardia	Believed to block pacemaker current

*Investigational.
†Flecainide and encainide have been withdrawn from use because of increased risk of sudden death in humans.
‡Class III drugs are being subclassified to include K^+ channel facilitators (pinacidil).
§Class V drugs will not be discussed.

TABLE 17–3
Sympathetic and Parasympathetic Effects of Antiarrhythmic Drugs

Drug	Sympathetic Effects	Parasympathetic Effects
Quinidine	α-Adrenoceptor blocker; β_1 stimulation?	Vagolytic
Procainamide	Ganglion blocking	
Disopyramide		Vagolytic
Lidocaine		
Tocainide		Same as lidocaine
Mexiletine		Same as lidocaine
Phenytoin	Sympatholytic CNS effect	
Propafenone	$\beta_{1,2}$-Adrenoceptor blocker	
Propranolol	$\beta_{1,2}$-Adrenoceptor blocker	
Nadolol	$\beta_{1,2}$-Adrenoceptor blocker	
Atenolol	β_1-Adrenoceptor blocker	
Metoprolol	β_1-Adrenoceptor blocker	
Esmolol	β_1-Adrenoceptor blocker (moderately cardioselective)	
Labetalol	$\beta_{1,2}$-Adrenoceptor blocker, α_1-adrenoceptor blocker	
Amiodarone	$\beta_{1,2}$-Adrenoceptor blocker, α_1-adrenoceptor blocker	
Bretylium	Initial norepinephrine release; late sympatholysis	
Sotalol	$\beta_{1,2}$-Adrenoceptor blocker	
Verapamil	α-Adrenoceptor blocker; noncompetitive sympatholytic	
Digitalis	Sensitizes baroreceptors; stimulates CNS; stimulates postganglionic sympathetic nerves; releases norepinephrine from sympathetic nerve terminals	Increases vagal tone

Modified from Muir WW III, Sams RA. Pharmacology and pharmacokinetics of antiarrhythmic drugs. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 309.

TABLE 17-4

Classification of Antiarrhythmic Drug Actions on Arrhythmias Based on Modification of Vulnerable Parameter

Arrhythmia	Mechanisms	Vulnerable Parameter	Drugs*
Inappropriate sinus tachycardia Some idiopathic ventricular tachycardia	Automaticity (A) Enhanced normal	Phase 4 depolarization (decrease)	β-adrenergic-blocking agents Na^+ channel-blocking agents
Accelerated idioventricular rhythms		Phase 4 depolarization (decrease)	Ca^{++} or Na^+ channel-blocking agents
Torsades de pointes	Triggered activity (A) EAD	Action potential duration (shorten) or EAD (suppress)	β-agonists; vagolytic agents (increase rate) Ca^{++} channel-blocking agents Mg^{++}; β-adrenergic-blocking agents
Digitalis-induced arrhythmias	(B) DAD	Calcium overload (unload) or DAD (suppress)	Ca^{++} channel-blocking agents Na^+ channel-blocking agents
Certain autonomically mediated ventricular tachycardias		Calcium overload (unload) or DAD (suppress)	β-adrenergic-blocking agents Ca^{++} channel-blocking agents, adenosine
Sustained monomorphic ventricular tachycardia		Conduction and excitability (depress)	Na^+ channel-blocking agents
Atrial fibrillation		Refractory period (prolong)	K^+ channel blockers
Polymorphic and sustained monomorphic ventricular tachycardia		Refractory period (prolong)	Quinidine, procainamide, disopyramide
Ventricular fibrillation		Refractory period (prolong)	Bretylium Amiodarone, sotalol
AV nodal reentrant tachycardia	Reentry (Ca^{++} channel-dependent)	Conduction and excitability (depress)	Ca^{++} channel-blocking agents

*Refer to Table 17-2.

EAD, early after depolarizations; DAD, delayed after depolarizations.

Modified from The Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. The Sicilian Gambit: a new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. Eur Heart J 12:1112, 1991.

rhythmias) is one of the more prominent therapeutic effects of calcium-blocking drugs, although this action is not characteristic of all drugs in this group.[24, 27] Diltiazem and perhaps verapamil to a lesser extent have emerged as the most clinically useful calcium-blocking drugs for the treatment of supraventricular arrhythmias (chapter 18).

CLINICAL PHARMACOKINETICS

The pharmacologic effects of most drugs affecting the cardiovascular system are assumed to be a function of the drug concentration at specific receptor sites within the body. Although drug concentrations at these sites are rarely measured, it is generally assumed that the concentration of drug at the receptor site ultimately attains equilibrium with the concentration of drug in the vascular system (i.e., blood or plasma). Therefore, the concentration of drug at the receptor site is affected by the same factors as those affecting the concentration of drug in the blood (namely, the rate and extent of absorption, distribution processes, metabolism, excretion, and protein binding). Furthermore, the development of safe and effective dosage regimens depends on elucidation of various pharmacokinetic parameters and knowledge of effective plasma concentrations of the drug. For example, the dose rate required to maintain an average or steady-state plasma drug concentration to produce a beneficial drug effect after attainment of equilibrium between drug in blood and at the receptor is obtained by the following equation:

$$\text{Dose rate} = \text{total body clearance} \times \text{average plasma drug concentration desired}$$

If the bioavailability of a drug is known after administration by a specific nonintravenous route, the dose rate should be modified by dividing the right-hand side of the equation by the extent of bioavailability. When the desired maximum and minimum plasma drug concentrations are known, the maximum time interval between doses (T) can be calculated:

$$T = 1.44 \times t_{1/2} \ln \left(\frac{\text{maximum drug concentration}}{\text{minimum drug concentration}} \right)$$

where $t_{1/2}$ is the terminal elimination half-life of the drug and ln is the natural logarithm.

The time required to achieve steady-state plasma drug concentrations after initiating constant intravenous infusion or multiple dosing is approximately four half-lives of the drug. If it is necessary or desirable to achieve therapeutic drug concentrations more rapidly, a loading dose can be given when the constant infusion or multiple dosing regimen is started. The loading dose is calculated as:

TABLE 17–5
Electrocardiographic Properties of Popular Antiarrhythmic Drugs

Drug	Sinus Rate	QRS Duration	QT Duration	Ventricular Response During Atrial Fibrillation	Ventricular Rate	Accessory Pathway	Supraventricular Arrhythmias	Ventricular Arrhythmia	Antifibrillatory
Quinidine	↑	↑	↑	↑	↓	↓	+ +	+ +	0
Procainamide	0	0/↑	0/↑	0	↓	↓	+	+ +	0
Lidocaine	0/↑	0	0/↓	0	↓	0/↓	0	+ + +	+
Tocainide	0/↑	0	0/↓	0	↓	0/↓	0	+ +	+?
Mexiletine	0/↑	0	0/↓	0	↓	0/↓	0	+ +	+?
Phenytoin	0	0	0	0	0	↓/0	0	+	0
Propafenone	↓	0	0	0	0/↓	↓ ↓	+	+ +	−
Propranolol	↓	0	0	↓	↓	↓	+	−	0
Atenolol	↓	0	0	↓	↓	↓	+	+	0
Esmolol	↓	0	0	↓	↓	↓	+	+	0
Amiodarone	↓	0	↑	↓	0	↓	+	+ +	+
Sotalol	↓	↑	↑	0/↓	0/↓	↓	+	+	+ +
Diltiazem	↓	0	0	↓ ↓	0	0/↓	+ +	+	0
Digoxin	↓	0	0	↓	0	0/↓	+ +	+	−
Glycopyrrolate	↑	0	0	↑	0	0	0	0	−

↑ = Increase; ↓ = decrease; 0 = no effect; + = beneficial effect; − = detrimental effect.
Modified from Muir WW III, Sams RA. Pharmacology and pharmacokinetics of antiarrhythmic drugs. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, pp 309–333.

$$\text{Loading dose} = \text{desired plasma drug concentration} \times \text{volume of distribution}$$

Drug concentrations immediately after intravenous bolus dose administration will be greater than desired if the drug is extensively distributed. Therefore, if the drug has a low therapeutic index, the loading dose should be divided or given slowly. Again, if bioavailability is incomplete, the appropriate correction can be made by dividing the right-hand side of the equation by the extent of bioavailability.

CLEARANCE AND VOLUME OF DISTRIBUTION

ORGAN CLEARANCE

Clearance and volume of distribution are the most important terms in defining the disposition of a drug. Individual organ clearances added together equal the total body clearance:

$$CL = CL_{renal} + CL_{liver} + CL_{other}$$

where CL represents clearance and the subscripts indicate the organ or process involved. "Others" may represent lung, saliva, sweat, and additional sites of metabolism. If it is known, for example, that the drug is eliminated primarily by hepatic metabolism, the total body clearance approximates hepatic clearance.

Individual organ clearances can be expressed as follows:

$$CL = \text{organ blood flow} \times \text{extraction ratio}$$

EXTRACTION RATIO

The extraction ratio is an expression of the fraction of the drug molecules entering the organ that are removed by the organ. The extraction ratio ranges from zero for a noneliminating organ to unity for an organ that removes all drug molecules entering the organ. The maximum clearance of an organ is therefore equal to the total blood flow to the organ.

EXAMPLE OF ORGAN CLEARANCE—HEPATIC

To illustrate the principles of clearance and the extraction ratio, the hepatic clearance of drug is used. The hepatic extraction ratio ($E_{hepatic}$) is approximated as follows:

$$E_{hepatic} = \frac{f_u \times CL_{intrinsic}}{Q_{hepatic} + f_u \times CL_{intrinsic}}$$

where f_u is the fraction of the drug unbound in blood, $CL_{intrinsic}$ is the intrinsic metabolic clearance, and $Q_{hepatic}$ is the total hepatic blood flow rate. Hepatic clearance is therefore approximated by the following equation:

$$CL_{hepatic} = Q_{hepatic} \frac{f_u \times CL_{intrinsic}}{Q_{hepatic} + f_u \times CL_{intrinsic}}$$

If hepatic blood flow is much greater than the product of unbound fraction and intrinsic clearance, hepatic clearance reduces to the following equation:

$$CL_{hepatic} = f_u \times CL_{intrinsic}$$

For drugs cleared in this manner, hepatic clearance is dependent on the unbound fraction and the intrinsic clearance, but it is relatively independent of liver blood flow rate. Therefore, hepatic clearance of such low-extraction drugs will be influenced or affected by drug interactions and disease processes that affect protein binding of drugs and their intrinsic clearances. Intrinsic clearance, in turn, depends on the properties of hepatic microsomal enzymes, which are subject to enzyme induction and enzyme inhibition.

In other cases in which the hepatic blood flow is less than the product of the unbound fraction and the intrinsic clearance, the hepatic clearance is approximated by the equation:

$$CL_{hepatic} = Q_{hepatic}$$

Therefore, hepatic clearances of such "high-extraction" drugs will depend only on hepatic blood flow rates. The clearances of these drugs (e.g., propranolol and lidocaine) will not be significantly affected by alterations in plasma protein binding or intrinsic clearance.

The extent of oral bioavailability is determined not only by the fraction of the dose that is absorbed but also by the fraction of the absorbed dose that escapes hepatic metabolism. The latter fraction is readily estimated from the expression:

$$F = 1 - E_{hepatic}$$

where F is the fraction of the absorbed dose escaping first-pass metabolism and $E_{hepatic}$ is the extraction ratio. First-pass metabolism of highly extracted drugs, such as lidocaine and propranolol, will be high, and the fraction escaping first-pass metabolism will be low. The converse is true for low-extraction drugs, such as phenytoin and tocainide.

VOLUME OF DISTRIBUTION

The volume of distribution is a measure of the extent of distribution of a drug outside the vascular compartment. Thus, a drug characterized by a large volume of distribution, such as lidocaine or digoxin, is extensively distributed to tissues, and a drug with a small volume of distribution, such as phenytoin, is not.

The volume of distribution (Vd_{ss}) depends on several physiologic parameters as follows:

$$Vd_{ss} = V_P + \{f_{u,p}/f_{u,t}\} \times V_T$$

where V_P is the volume of plasma water, $f_{u,p}$ is the fraction of drug not bound to plasma proteins, $f_{u,t}$ is the fraction of drug not bound to tissue components, and V_T is the volume of water in the tissues. The volume of distribution of a drug will therefore be altered by changes in plasma and tissue volumes and by changes in the extent of drug binding to plasma proteins and tissue components. Several diseases cause alterations in binding, and drug interactions often involve competition between drugs for binding sites on plasma proteins or tissue components.

DRUG HALF-LIFE

The half-life of a drug is a useful pharmacokinetic parameter that depends on the volume of distribution and the total body clearance as shown:

$$\text{Half-life} = 0.693 \times Vd_{ss}/CL$$

Thus, an increase in the volume of distribution or a decrease in total body clearance will increase the half-life of a drug. Since both changes may occur in various disease states, the change in half-life may be greater than that predicted on the basis of an evaluation of a change in either the volume of distribution or the total body clearance alone.

PHARMACOLOGY OF SPECIFIC ANTIARRHYTHMIC DRUGS

QUINIDINE

CLINICAL USE

Quinidine can be used to treat either supraventricular or ventricular arrhythmias in dogs. Although it has been administered most often for ventricular arrhythmias, its use and popularity have waned when compared with more current antiarrhythmic agents. Occasionally in the dog it may be of value in the treatment of acute atrial fibrillation, particularly when this arrhythmia is not associated with atrial enlargement.

ELECTROPHYSIOLOGY AND ELECTROCARDIOGRAPHY

Quinidine is the prototypic Class Ia antiarrhythmic drug. Like all Class I antiarrhythmic drugs (see Table 17–2), quinidine produces membrane-stabilizing effects resulting from its inhibition of transmembrane sodium flux.[8, 33–35] The decrease in transmembrane sodium flux results in depression of conduction of electrical impulses and membrane responsiveness. Prolongation of the action potential is a cellular electrophysiologic effect shared by quinidine and other Class Ia and III antiarrhythmic drugs (see Table 17–2). This action, combined with quinidine's ability to depress conduction, results in a marked prolongation of the effective refractory period in cardiac tissues. These direct cellular electrophysiologic effects are believed to be the primary mechanisms responsible for the antiarrhythmic efficacy of quinidine but are known to be extremely dependent on serum potassium concentrations.[33, 34, 36] Low serum potassium concentrations antagonize the depressant actions of quinidine, whereas high serum concentrations increase quinidine's depression of conduction velocity, membrane responsiveness, and automaticity.

Clinically, quinidine's effects are the result of direct and indirect actions mediated by competitive blockade of muscarinic cholinergic receptors (see Table 17–3). Changes in heart rate and rhythm are dependent on the prevailing parasympathetic tone and the type of arrhythmia being treated (supraventricular versus ventricular). Since the parasympathetic nervous system innervates supraventricular tissues and proximal portions of the His-Purkinje system, quinidine's anticholinergic actions may increase SA node automaticity and AV conduction (see Tables 17–3 and 17–5).

At therapeutic concentrations, the direct and indirect electrophysiologic actions of quinidine cause some alterations in the electrocardiogram. Minimal to moderate increases in sinus rate, slight increases in QRS duration, and prolongation of the QT interval can develop. The PR interval usually remains unchanged.[37] Acceleration of AV nodal conduction is an important consideration when treating patients with atrial fibrillation and flutter because of the potential to produce marked increases in ventricular rate. Clinically, digitalis has been added to slow AV conduction and prevent increases in ventricular rate in patients with supraventricular arrhythmias, especially atrial fibrillation. However, calcium channel blockers may be more beneficial in such circumstances.[38] Toxic plasma concentrations of quinidine generally produce prolongation of the PR interval and QRS duration. An increase in the QRS duration of more than 25 percent is indicative of quinidine toxicity.

PHARMACOKINETICS

Quinidine is a lipophilic weak base (pK_a 4.0 and 8.6) that is rapidly and widely distributed to peripheral tissues. It is extensively bound to plasma and tissue proteins and has a large volume of distribution.[39]

Quinidine is eliminated by the kidneys and is metabolized by the liver; less than 40 percent of the dose is

eliminated unchanged in the urine.[39, 40] Since hepatic clearance (4.1 ml/min/kg) is less than hepatic blood flow, hepatic clearance is relatively insensitive to changes in hepatic blood flow but is sensitive to changes in binding and intrinsic clearance. For example, propranolol does not reduce quinidine clearance in spite of a reduction in hepatic blood flow.[41] The oral availability of quinidine is good and is not appreciably influenced by first-pass metabolism.

Quinidine competes for tissue-binding sites of certain drugs, most notably digoxin. Consequently, plasma digoxin concentrations rise during quinidine therapy due to displacement of digoxin from skeletal muscle and other tissue-binding sites.[42, 43] Furthermore, quinidine reduces the renal clearance of digoxin by unknown mechanisms.[42, 43] The possibility of central nervous system–induced toxicity with arrhythmia production due to an increased circulating plasma concentration of digoxin has also been suggested.[44] Thus, plasma digoxin concentrations should be monitored during combined quinidine-digoxin therapy and the digoxin dosage reduced if necessary.

SIDE EFFECTS AND TOXICITY

Negative inotropism, vasodilation, and hypotension can be produced by quinidine when administered at therapeutic dosages. These hemodynamic actions are not a problem in patients with normal cardiac function but must be considered when treating patients with compromised or compensated cardiac disorders. Quinidine produces vasodilation by blocking both α_1- and α_2-adrenoceptors.[45]

Toxic quinidine concentrations produce a variety of deleterious cardiac effects that are extensions of its direct electrophysiologic and hemodynamic actions. First-, second-, and third-degree AV block, intraventricular (i.e., bundle branch) block, and ventricular tachycardia can be produced by quinidine. Ventricular premature complexes are probably produced by marked depression of conduction of electrical impulses, or are due to quinidine's ability to induce early afterdepolarizations.[46, 47] Direct depression of cardiac contractility and vasodilation cause decreases in cardiac output, hypotension, and increases in left ventricular end-diastolic pressure. Clinically, these changes are recognized by the development of lethargy, weakness, and pulmonary edema. Sodium bicarbonate, 1 mg/kg IV, can be used to partially reverse cardiotoxicity and hypotension (Table 17–6). Metabolic alkalosis can temporarily decrease serum potassium concentrations, thereby limiting quinidine's direct cellular effects, and increase quinidine's binding to serum albumin. Protein-bound drugs do not exert pharmacologic activity.

Nausea, vomiting, and diarrhea are the most frequently encountered adverse effects associated with oral quinidine therapy in dogs and cats. Approximately 25 percent of all dogs treated with oral quinidine develop signs suggestive of gastrointestinal discomfort (Muir and Sams, unpublished data). Gastrointestinal side effects may be greater in cats, although quinidine is rarely used in this species.

PROCAINAMIDE

CLINICAL USE

Procainamide has actions that affect both atrial and ventricular tissues. Therefore, it can be used in the treatment of supraventricular and ventricular arrhythmias. Although it is similar to quinidine, it is used more successfully in the treatment of ventricular arrhythmias, with fewer side effects (see Table 17–6).

ELECTROPHYSIOLOGY AND ELECTROCARDIOGRAPHY

Procainamide is a Class Ia antiarrhythmic drug with electrophysiologic properties similar to those of quinidine.[35] Like quinidine, its electrophysiologic effects are due both to direct and indirect (anticholinergic) actions (see Tables 17–2, 17–3).[8, 35] Studies in animals yield conflicting results with regard to the effect of procainamide on sinus heart rate.[48] At low drug concentrations there is a vagolytic action, and at high drug concentrations there is a direct depressant effect. Studies in dogs reveal that in a dose-dependent manner AV nodal conduction and His-Purkinje conduction are prolonged, and the refractory periods of the atrial and ventricular muscles are prolonged.[48] The direct depression of the AV node conduction velocity and the prolongation of refractoriness are partially blunted by the anticholinergic effects. Clinically, anticholinergic effects may be responsible for increases in ventricular rate caused by an increase in the transmission of atrial impulses through the AV node. Therapeutic doses of procainamide, however, generally produce little or no effect on AV nodal conduction velocity or refractoriness in patients in normal sinus rhythm.

Atrial automatic tissues are more sensitive than are ventricular automatic tissues as procainamide suppresses normal and abnormal automaticity.[49] Procainamide's effect on automaticity is believed to be its primary antiarrhythmic effect.[49] It depresses the rate of rise of phase 0 of the action potential, resulting in decreased conduction velocity of electrical impulses in all cardiac tissues. Procainamide depresses membrane responsiveness and excitability in atrial and ventricular specialized fibers and muscle.[8] The vagolytic effects of procainamide on supraventricular tissues (particularly the AV node) are less pronounced than those of quinidine. The electrophysiologic effects of procainamide, like those of quinidine, depend on the extracellular

TABLE 17-6
Therapeutic Guidelines and Adverse Effects of Antiarrhythmic Drugs*

Drug	Trade Name	Dose* and Route of Administration	Adverse Effects: *Electrophysiologic*	Adverse Effects: *Hemodynamic*	Adverse Effects: *Other*
Quinidine	Quinidine sulfate Quinidine gluconate Quinidine Dura-tabs	5–15 mg/kg qid PO 6–20 mg/kg tid-qid PO, IM	Aggravation of arrhythmia, AV block; increased ventricular response in A fib	Mild negative inotrope, hypotension	Nausea, vomiting, diarrhea, depression
Procainamide	Pronestyl Procan SR	10–20 mg/kg qid PO; 8–20 mg/kg IV, IM; 20–50 μg/kg/min CRI† 20–50 mg/kg tid PO; cat: 62.5 mg/cat bid–tid PO	Arrhythmia aggravation; AV block	Hypotension with IV use	Anorexia, nausea, vomiting, lupus-like reaction
Disopyramide	Norpace	10–20 mg/kg q2h PO	Arrhythmia aggravation; AV block; increase in ventricular rate in A fib	Aggravates CHF; hypotension	
Lidocaine	Lidocaine	2–8 mg/kg IV over 10 min 40–80 μg/kg/min IV CRI† (cats: 0.25–1 mg/kg IV over 5 min)	Arrhythmia aggravation Sinus bradycardia AV block	Minor	Drowsiness, ataxia, nystagmus, tremor, vomiting, seizures
Tocainide	Tonocard	10–20 mg/kg tid PO	Same as lidocaine	Same as lidocaine	Same as lidocaine
Mexiletine	Mexitil	2–8 mg/kg bid-tid PO	Same as lidocaine	Same as lidocaine	Same as lidocaine
Phenytoin	Dilantin	30 mg/kg tid PO 10 mg/kg IV slowly	Minor	Minor	Depression, seizures
Propafenone	Rhythmol	3–10 mg/kg tid PO	Bradycardia, arrhythmia aggravation	Hypotension, negative inotrope	Depression
Propranolol	Inderal	5–40 mg tid PO 0.01–0.3 mg/kg IV; cat: 0.2–1.0 mg/kg tid PO; 0.04–0.06 mg/kg IV slowly	Bradycardia; AV block	Negative inotrope; hypotension	Depression, aggravation of pulmonary bronchoconstriction
Nadolol	Corgard	5–40 mg tid PO			
Atenolol	Tenormin	0.5–1.0 mg/kg sid or bid PO; cat: 6.25–12.5 mg sid-bid PO			
Metoprolol	Lopressor	5–50 mg tid PO			
Esmolol	Brevibloc	50–100 μg/kg/min slowly IV to effect			
Amiodarone	Cordarone	5–15 mg/kg bid PO	Bradycardia; AV block	Negative inotrope; hypotension	Hypothyroidism, hyperthyroidism, pulmonary fibrosis, photosensitization, liver failure
Bretylium	Bretylol	5–10 mg/kg IV	Arrhythmia aggravation; tachycardia	Hypotension (late)	Nausea, vomiting
Sotalol	Betapace	0.5–2 mg/kg bid, tid; PO	Bradycardia, AV block, arrhythmia aggravation	Negative inotrope, hypotension	Depression
Verapamil	Calan; Isoptin	1–5 mg/kg tid PO; 0.05 mg/kg q 10–30 min IV (maximum cumulative dose is 0.15 mg/kg)	Bradycardia; AV block hypotension	Negative inotrope	Depression
Diltiazem	Cardiazem	0.5–2 mg/kg tid PO; 1–5 μg/kg/min IV	Bradycardia; AV block; hypotension	Negative inotrope	Minimal depression
Adenosine	Adenocard	1–2 mg IV rapidly; repeat if necessary	AV block; bradycardia	Hypotension	Depression
Digoxin	Lanoxin	0.005–0.011 mg/kg IV 0.22 mg/m² bid PO, or 0.1 mg/kg divided bid PO; cat: 0.031 mg q 24–48 h PO	Sinus bradycardia; AV block; proarrhythmia	Positive inotrope	Vomiting, diarrhea
Atropine sulfate	Atropine	0.02–0.04 mg/kg SQ, IV	Tachycardia; ventricular arrhythmias	Increased MVO_2	Depression, constipation
Glycopyrrolate	Robinul-V	0.005–0.01 mg/kg SQ, IV	Tachycardia	Increased MVO_2	Constipation

*All doses are for the dog, unless otherwise indicated.
†CRI, constant rate infusion; formula for CRI: Body weight (kg) × dose (μg/kg/min) × 0.36 = total dose in milligrams administered IV over 6 hours.
MVO_2, myocardial oxygen consumption; A fib, atrial fibrillation; CHF, congestive heart failure.
Modified from Muir WW III, Sams RA. Pharmacology and pharmacokinetics of antiarrhythmic drugs. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, pp 309–333.

potassium ion concentration. Increases in extracellular potassium potentiate its depressant actions.

Therapeutic dosages of procainamide produce ECG changes that are the result of the direct cellular electrophysiologic effects of the drug. Sinus rate remains unchanged or is minimally decreased. The PR, QRS, and QT intervals are minimally prolonged (see Tables 17–5, 17–6). The magnitudes of these changes are determined by the plasma concentration of procainamide and can be used to monitor toxic drug concentrations. A 25 percent increase in the QRS interval is an indication of procainamide toxicity.

PHARMACOKINETICS

Procainamide is a lipophilic weak base (pK 9.23) that is structurally related to procaine. Procainamide is rapidly and extensively distributed to extravascular tissues and, consequently, has a volume of distribution greater than that of total body water.[50] Procainamide is metabolized by the liver and excreted by the kidney. Renal excretion of procainamide is proportional to creatinine clearance. *N*-Acetylprocainamide, an active metabolite of procainamide in humans, is not produced in dogs or cats.[51] Drugs or diseases that interfere with liver metabolism or increase serum creatinine concentration should be expected to prolong procainamide elimination.

Total body clearance of procainamide in dogs is about 7 to 9 ml/min/kg at dosages of 8 to 26 mg/kg.[51] The relative contributions of renal and hepatic clearance to total clearance are unknown. If total clearance is due largely to hepatic metabolism, then it would be expected that alterations in liver blood flow would have little effect on total clearance since procainamide has a low extraction ratio.

Plasma procainamide concentrations that are effective against ventricular arrhythmias produced by digitalis intoxication in dogs range from about 25 to 50 μg/ml (Davis LE, personal communication). These concentrations are higher than in persons, perhaps due to the contribution of *N*-acetylprocainamide to the pharmacologic effect in humans. These plasma concentrations can be attained with loading doses of 38.2 mg/kg, followed by constant rate infusions of 16.3 mg/kg/hr. Plasma procainamide concentrations effective for controlling arrhythmias produced by coronary occlusion and digitalis intoxication in dogs have also been achieved after intravenous doses of 40 to 60 mg/kg.[51] However, plasma procainamide concentrations required to abolish clinical arrhythmias are much lower than 25 to 50 μg/ml.

SIDE EFFECTS AND TOXICITY

Procainamide produces minimal cardiovascular depressant effects when compared with quinidine.[52] Mild depression of cardiac contractility, vasodilation, and hypotension are produced when therapeutic dosages of procainamide are administered intravenously. Intramuscular and oral administration of procainamide produce insignificant changes in hemodynamics in dogs with normal myocardial function. Myocardial depression following procainamide administration to patients in heart failure is minimal, a function of dosage, and dependent on the rate and route of drug administration.

Toxic dosages of procainamide produce hypotension and marked depression of AV conduction (see Table 17–6). First-, second-, or third-degree AV block can occur. Depressed conduction in atrial and ventricular specialized fibers may initiate intraventricular block, precipitate tachyarrhythmias, or exacerbate existing arrhythmias. The precipitation of tachyarrhythmias by toxic dosages of procainamide or quinidine can result in syncope or lead to the sudden development of ventricular fibrillation.[53] Clinically, prolongation of the QRS and QT intervals (corrected for changes in heart rate) can be used as a therapeutic guide in order to avoid toxicity. Hypotension can be treated by the administration of fluids, calcium-containing solutions, or catecholamines (e.g., dopamine, dobutamine).

Patients receiving oral procainamide occasionally develop nausea, vomiting, and diarrhea. These gastrointestinal side effects are infrequent and generally subside when therapy is discontinued or reduced. A side effect that does not appear to be associated with adverse consequences occurs in some black dogs treated with procainamide. Black Dobermans and brindle boxers have turned reddish brown when treated with procainamide (Moïse NS, unpublished observations).

DISOPYRAMIDE

CLINICAL USE

Disopyramide is used less commonly than quinidine and procainamide in the treatment of ventricular arrhythmias.[54] Unfortunately, side effects have limited its use in dogs.[55]

ELECTROPHYSIOLOGY AND ELECTROCARDIOGRAPHY

Disopyramide is a Class Ia antiarrhythmic drug with electrophysiologic and ECG properties similar to those of quinidine and procainamide (see Table 17–2).[8, 36] Disopyramide has a long duration of action and produces few side effects in humans.[54] Like quinidine and procainamide, disopyramide produces electrophysiologic actions that are due to direct and indirect (i.e., anticholinergic) effects[55, 56] (see Table 17–3). Unlike quinidine and procainamide, however, the anticholin-

ergic effects of disopyramide predominate at relatively low plasma concentrations. This results in increases in sinus rate and acceleration of AV conduction when therapeutic dosages of disopyramide are administered. Disopyramide should be used cautiously in patients with atrial flutter or fibrillation in order to prevent excessive ventricular rates. Disopyramide produces decreases in automaticity and conduction velocity, and increases in refractoriness. Large doses of disopyramide produce direct depression of AV conduction. These actions are dependent on the extracellular potassium concentration. Like quinidine and procainamide, disopyramide produces dose-dependent prolongation of the PR, QRS, and QT intervals (see Tables 17–5 and 17–6).

PHARMACOKINETICS

Disopyramide is a lipophilic weak base (pK_a 8.36) that is rapidly and extensively distributed to extravascular tissues. The binding of disopyramide to plasma α_1-acid glycoprotein is concentration dependent and consequently the volume of distribution varies with concentration.[57]

Disopyramide is cleared by renal and hepatic mechanisms, with approximately 20 percent of an intravenous dose eliminated unchanged in the urine. Hepatic metabolism is extensive and involves successive *N*-dealkylation.[57, 58] Metabolites may contribute to the overall pharmacologic effect. Hepatic clearance is intermediate in magnitude between that of quinidine and propranolol.

Oral bioavailability is incomplete due to first-pass metabolism and averages about 40 percent. The half-life is somewhat larger after oral dosing (2.4 hours) than after intravenous doses (1.1 hours).[57]

Disopyramide doses of 3 to 5 mg/kg IV slow the sinus rate in healthy dogs.[59] Maximum plasma concentrations after such doses are approximately 2 to 5 μg/ml. Frequent dosing is required owing to the rapid clearance and short half-life in the dog.

SIDE EFFECTS AND TOXICITY

Therapeutic dosages of disopyramide produce significant decreases in myocardial contractility.[60] This effect is much more pronounced than with quinidine and procainamide and can lead to a reduction in cardiac output and an increase in left ventricular end-diastolic pressure. Disopyramide therapy also produces vasoconstriction, resulting in an increase in peripheral vascular resistance. The mechanism for this latter effect is controversial but may increase afterload, resulting in a reduction in cardiac output. The deleterious cardiovascular effects of disopyramide are dose dependent and must be given serious consideration in patients with cardiac arrhythmias and heart failure.[61]

The toxic manifestations associated with disopyramide therapy are primarily attributed to hypotension and myocardial depression, although electrophysiologic and ECG abnormalities similar to those produced by quinidine and procainamide can be expected (see Tables 17–5, 17–6).[46] Lethargy, weakness, and syncope may occur. Pulmonary congestion may develop or be exacerbated if dogs with compensated heart failure are treated with excessive doses of disopyramide. Anticholinergic actions may result in tachycardia. The incidence of severe adverse side effects during long-term disopyramide therapy in dogs and cats is unknown.

LIDOCAINE

CLINICAL USE

Lidocaine is relatively ineffective in the treatment of supraventricular arrhythmias but is very effective for the treatment of ventricular arrhythmias in dogs and cats (chapters 18 and 19). Nonsustained and sustained ventricular tachycardia, monomorphic and polymorphic ventricular tachycardia, ventricular arrhythmias caused by cardiac sensitization to catecholamines (halothane), and digitalis toxicity respond favorably to lidocaine therapy.[53] Lidocaine should be considered the drug of choice for the acute treatment of ventricular arrhythmias in patients with compensated or uncompensated heart failure, but it should be used cautiously in order to avoid hypotension.[7, 61, 62]

ELECTROPHYSIOLOGY AND ELECTROCARDIOGRAPHY

Lidocaine is a local anesthetic and Class Ib antiarrhythmic drug that produces minimal depression of phase 0 of the cardiac action potential in normal tissue but marked depression of phase 0 in diseased tissues.[63, 64] Unlike Class Ia antiarrhythmic drugs (i.e., quinidine, procainamide, disopyramide), therapeutic concentrations of lidocaine produce little effect on sinus rate, AV conduction, or action potential duration and refractoriness. Therefore, lidocaine usually can be effectively used in patients with SA node dysfunction.[65] Lidocaine does not produce anticholinergic effects.[66] Cardiac muscle membrane responsiveness, excitability, and conduction velocity are depressed to a lesser degree by therapeutic concentrations of lidocaine than by quinidine or procainamide. In contrast to Class Ia antiarrhythmic drugs, lidocaine shortens action potential duration in atrial and ventricular specialized fibers, although the effective refractory period may be prolonged slightly.[53] Lidocaine does not alter atrial refractoriness and conduction velocity, which may be a partial explanation for its ineffectiveness in the treatment of supraventricular arrhythmias.

The cellular electrophysiologic effects of lidocaine depend on the extracellular potassium concentration.[7] Hyperkalemia intensifies depressant effects on cardiac membranes, whereas hypokalemia diminishes its effectiveness.[36]

Lidocaine generally produces no change in PR, QRS, or QT duration. The QT interval may decrease somewhat due to the ability of lidocaine to shorten action potential duration. Occasionally, lidocaine produces sinus tachycardia (see Table 17–5). The mechanism for this latter effect is uncertain, but it may involve the central nervous system.

PHARMACOKINETICS

Lidocaine is a highly lipophilic weak base (pK_a 7.85) that is rapidly and extensively distributed to extravascular tissues. Consequently, it has a very large volume of distribution. Lidocaine binds (44 to 71 percent) to plasma proteins, primarily α_1-acid glycoprotein.

Lidocaine cannot be used orally despite excellent oral absorption.[60] The clearance of lidocaine from plasma is very high (first-pass effect) and is attributed to hepatic metabolism, since only about 2 percent of an intravenous dose is recovered unchanged in the urine.[67, 68] Major metabolites result from successive *N*-dealkylation and aromatic ring hydroxylation.[67] The *N*-dealkylated metabolites are pharmacologically active, possibly contributing to the antiarrhythmic and toxic effects of lidocaine.

Lidocaine is rapidly metabolized by the liver. Consequently, its hepatic metabolism is dependent upon liver blood flow.[62] Therefore, patients in heart failure clear lidocaine more slowly than normal patients and require correspondingly lower dosages. Propranolol[69] and cimetidine reduce hepatic blood flow. If administered concurrently with lidocaine, these drugs could decrease lidocaine clearance and predispose to lidocaine toxicity.[70, 71] Therapeutic plasma lidocaine concentrations in persons range from 2 to 4 μg/ml, with toxicity occurring at concentrations as low as 5 to 9 μg/ml.[72] Concentrations in excess of 9 μg/ml in humans are frequently associated with toxicity. Ouabain-induced ventricular arrhythmias in dogs are abolished at a mean concentration of 6.2 μg/ml.[7] Plasma concentrations required to abolish spontaneously occurring arrhythmias range from 0.5 to 4.0 μg/ml.

SIDE EFFECTS AND TOXICITY

Therapeutic doses of lidocaine produce minimal depression of cardiac contractility.[66] Intravenous bolus administrations or infusions of large dosages can produce transient and mild reductions in cardiac contractility and vasodilation that may result in transient decreases in cardiac output and arterial blood pressure, respectively. Slow bolus injections of therapeutic doses of lidocaine to dogs in heart failure produce no change in cardiac output, blood pressure, or heart rate.[73, 74]

Central nervous system (CNS) excitement is the most common toxic side effect following intravenous lidocaine administration to dogs and cats (see Table 17–6).[75] Drowsiness and depression may occur when therapeutic doses of lidocaine are administered but are considered inconsequential. More frequently, agitation, disorientation, muscle twitching, nystagmus, and generalized tonic-clonic seizures are observed as the dose of lidocaine is increased. Convulsions are self-limiting and subside as the plasma lidocaine concentration decreases. Cats are more sensitive to the CNS side effects of lidocaine than are dogs, emphasizing the need for caution during intravenous bolus administration (Muir and Sams, unpublished data). Diazepam, 0.5 mg/kg, is effective in preventing lidocaine-induced seizures. Respiratory depression and respiratory arrest may occur in unconscious dogs and cats receiving lidocaine to control arrhythmias due to traumatic myocarditis (Muir and Sams, unpublished data).

TOCAINIDE

Tocainide is effective in the treatment of ventricular arrhythmias. However, its widespread use is limited because of side effects.[76]

ELECTROPHYSIOLOGY AND ELECTROCARDIOGRAPHY

Tocainide, an analogue of lidocaine, is a Class Ib antiarrhythmic drug (see Table 17–2).[8, 13, 24, 63] Tocainide is a lidocaine-like drug that can be given orally. Its electrophysiologic, antiarrhythmic, electrocardiographic, hemodynamic, and toxic effects are identical to those of lidocaine (see Tables 17–4 and 17–6).[70] Unlike lidocaine, however, tocainide's clearance is not significantly influenced by changes in liver blood flow, thereby negating the potential interactions with drugs like propranolol and cimetidine.

PHARMACOKINETICS

Tocainide is a lipophilic weak base structurally related to lidocaine. Tocainide was synthesized in an effort to produce an antiarrhythmic agent with a lower clearance and greater oral availability than those of lidocaine. The volume of distribution is greater than total body water but substantially less than that of lidocaine. Total body clearance of tocainide is less than 10 percent of that of lidocaine and is attributed to both hepatic metabolism and renal excretion.[77] Approximately 30 percent of an intravenous dose is elimi-

nated unchanged in the urine.[77] Hepatic clearance is approximately 2.9 ml/min/kg in healthy dogs[77] and is expected to be relatively insensitive to changes in hepatic blood flow. Tocainide is well absorbed after oral administration and is not extensively metabolized on its first pass through the liver.[78] This allows the drug to be given orally. The half-life of tocainide is approximately 4.7 hours after intravenous dosing and ranges from 8 to 12 hours after oral doses.[78]

SIDE EFFECTS AND TOXICITY

The high incidence of side effects (40 percent) (Muir and Sams, unpublished data) must be appreciated if tocainide is used. Nausea, vomiting, and anorexia are common; neurologic disturbances, including ataxia, disorientation, and twitching, can occur. Moreover, renal failure and ocular lesions develop with use for more than 6 months.[76]

MEXILETINE

Currently, mexiletine is the most commonly used oral Class Ib antiarrhythmic for the treatment of ventricular arrhythmias.[79-82] Preliminary experience and limited studies have shown it to be effective with a tolerable incidence of side effects. Mexiletine can be combined with β-adrenergic blockers (e.g., atenolol) to increase its effectiveness and potentially decrease side effects. Mexiletine has electrophysiologic, antiarrhythmic, ECG, hemodynamic, and toxic effects similar to those of lidocaine and tocainide (see Tables 17–2, 17–5, 17–6).[63, 83]

PHARMACOKINETICS

Mexiletine is rapidly absorbed from the gastrointestinal tract. A basic drug with high lipid solubility, it is metabolized by the liver and excreted by the kidney.[84] Renal excretion is dependent on urinary pH, leading to large variations in the plasma elimination half-life. The elimination half-life of mexiletine varies from 4.5 to 7 hours in dogs and is longer when the urine pH is alkaline.[85] Mexiletine is metabolized by hepatic mixed-function oxidases and, as with lidocaine, metabolism is influenced by liver blood flow. Cimetidine decreases the rate of mexiletine elimination. The volume of distribution of mexiletine is large due to its high lipid solubility. Therapeutic plasma concentrations range from 0.5 to 2 μg/ml.

SIDE EFFECTS AND TOXICITY

Dogs treated with mexiletine may become anxious or depressed. Twitching may develop. Some dogs become lethargic. Most side effects can be controlled by lowering the dose and combining treatment with a β-blocker or cautiously adding a Class Ia antiarrhythmic.

PROPAFENONE

CLINICAL USE

Propafenone, a Class Ib antiarrhythmic, is used in the treatment of ventricular and supraventricular tachycardia. It can be effective in preventing paroxysmal atrial fibrillation and flutter. Currently, the limiting factor in its use is the cost.

ELECTROPHYSIOLOGY AND ELECTROCARDIOGRAPHY

Propafenone possesses 1/40 the β-blocking activity of propranolol. However, because of propafenone's ability to decrease the maximum rate of rise of phase 0 of the cardiac action potential, it has been categorized as a Class Ib antiarrhythmic (see Table 17–2).[13] Propafenone-induced depression of phase 0 is observed in all cardiac tissues and is rate dependent, being more pronounced at higher heart rates. Concurrent with depression of phase 0, propafenone shortens action potential duration and decreases the rate of phase 4 diastolic depolarization in specialized atrial and Purkinje fibers. Propafenone slows the rate of depolarization of action potentials within the atrioventricular node, thereby slowing AV nodal conduction. This electrophysiologic profile predisposes patients to first-, second-, and third-degree atrioventricular block and prolongation of the QRS duration (see Table 17–5). Moreover, care should be used in treating patients with sick sinus syndrome.[86] Propafenone's mild, nonspecific β-blocking activity is responsible for its ability to slow sinus rate in intact animals.[8, 86]

PHARMACOKINETICS

Propafenone is absorbed slowly after oral administration, reaching peak serum concentrations within 2 to 5 hours of administration. Propafenone is extensively metabolized by the liver, and liver metabolites are known to contain varying degrees of parent compound activity. Oral dosages in dogs range from 3 to 10 mg/kg administered two or three times daily.

SIDE EFFECTS AND TOXICITY

Therapeutic concentrations of propafenone produce minimal decreases in arterial blood pressure and cardiac contractility, and caution should be used when administering propafenone as antiarrhythmic therapy to patients with congestive heart failure. Large doses may precipitate heart failure in patients with preex-

isting cardiovascular disease. Side effects include neurologic disorders, weakness, depression, nausea, and vomiting.[8] The potential for atrioventricular block must be considered, particularly in patients with preexisting atrioventricular conduction disturbances. Propafenone has the potential to produce proarrhythmic effects in patients that are hypokalemic or receiving large doses of loop diuretics (furosemide).[6, 87]

PROPRANOLOL

CLINICAL USE

Propranolol is used to treat sinus tachycardia, supraventricular and ventricular arrhythmias, hypertrophic cardiomyopathy, hypertension, hyperthyroidism, and pheochromocytoma.[88] Therapy with propranolol is greatly influenced by the prevailing sympathetic tone and β-adrenoceptor numbers. Chronic stimulation of cardiac receptors by the adrenergic nervous system or catecholamines in heart failure can result in a decrease in β-adrenoceptor numbers, known as *down regulation.* The administration of propranolol or any other β-adrenoceptor-blocking drug to a patient that has become dependent on adrenergic tone in order to maintain heart rate and cardiac contractility can be lethal. By contrast, receptor up regulation may occur during chronic therapy with propranolol and other β-adrenoceptor-blocking drugs. Chronic therapy with propranolol, for example, causes an increase in adrenergic receptor numbers or affinity (*up regulation*), resulting in severe cardiac arrhythmias should therapy be suddenly discontinued.[89] Similarly, patients with chronic hyperthyroidism demonstrate an increased number and sensitivity of β-receptors.

Propranolol is contraindicated with sinus bradycardia, AV block, and severe congestive heart failure. Patients with chronic obstructive airway disease, those undergoing anesthesia, or those receiving calcium entry-blocking drugs must be monitored closely if propranolol therapy is being considered.

Drugs other than propranolol that possess β-adrenoceptor-blocking activity are potentially useful for the treatment of cardiac arrhythmias in dogs and cats. Metoprolol, atenolol, and esmolol are cardioselective β_1-adrenoceptor-blocking drugs (Table 17–7) that offer specific advantages in patients with bronchospastic disorders or insulin-dependent diabetes mellitus.

ELECTROPHYSIOLOGY AND ELECTROCARDIOGRAPHY

Propranolol and compounds that possess β-adrenoceptor-blocking activity as their principal pharmacologic effect are grouped together as Class II antiarrhythmic drugs.[52] Beta-blocking drugs (see Tables 17–2 to 17–5) produce their beneficial effects on heart rate and rhythm by inhibiting the endogenous effects of the sympathetic nervous system or the effects of exogenously administered adrenergic drugs (e.g., norepinephrine, epinephrine, isoproterenol, dopamine, and dobutamine).[88] Adrenergic stimulation of the heart increases sinus rate, enhances conduction velocity through the AV node, and decreases refractoriness. Automaticity in atrial and ventricular specialized fibers is enhanced. Differential decreases in ventricular muscle refractoriness produce an inhomogeneous pattern of repolarization that, in the setting of increased automaticity, can predispose to arrhythmias. Propranolol and other β-adrenoceptor-blocking drugs slow sinus rate, depress conduction through the AV node, and produce a more homogeneous pattern of repolarization (see Table 17–5). Increases in automaticity produced by increases in sympathetic tone are abolished. Dosages of propranolol that produce plasma concentrations in the high therapeutic range (>100 ng/ml) cause direct cellular electrophysiologic effects. These direct actions are characteristic of the Class Ia antiarrhythmic drugs and have been referred to as quinidine-like effects.[83] The importance of quinidine-like effects during clinical therapy is controversial but unlikely to be significant. The electrocardiogram is minimally affected by propranolol, except for those changes induced by decreased heart rate and slowed AV conduction (see Table 17–5).

PHARMACOKINETICS

Propranolol is a lipophilic weak base (pK_a 9.45) that is highly bound to plasma α_1-acid glycoprotein (90 percent bound) and tissue proteins.[90] Consequently, propranolol is widely and extensively distributed to extravascular tissues and has a large volume of distribution (greater than total body water).[91]

Propranolol is metabolized in the liver to several oxidation products and their conjugates, which are eliminated in the urine.[92, 93] One of these oxidation products, 4-hydroxypropranolol, exhibits pharmacologic activity similar to that of propranolol and may contribute to propranolol's pharmacologic effect.[93]

Hepatic metabolism of propranolol is rapid and extensive (i.e., clearance is not affected by alterations in plasma protein binding or metabolic activity), perfusion rate-limited (i.e., clearance is affected by alterations in liver blood flow rate), and saturable. Consequently, the extraction ratio is high and dose dependent; only a small fraction of an oral dose escapes first-pass metabolism and reaches the systemic circulation.[94, 95] Therefore, oral bioavailability is low but may increase disproportionately with increased doses as saturation of liver enzymes occurs.

The total body clearance of propranolol is very high, approaching or perhaps exceeding liver blood flow in

TABLE 17-7
Pharmacologic Properties of β-Adrenoceptor-Blocking Drugs

Drug	Relative β_1 Selectivity	Intrinsic Sympathomimetic Activity	Lipophilicity	Membrane-Stabilizing Activity
Propranolol	0	0	High	+
Nadolol	0	0	Low	0
Timolol	0	0	Low	0
Pindolol	0	+	Moderate	+
Metoprolol	+	0	Moderate	0
Atenolol	+	0	Low	0
Esmolol*	+	0	?	0
Labetalol†	0	0	Low	0

*Short duration of action (10 to 20 minutes).
†Possesses α_1-adrenoceptor-blocking activity.
+, Property exhibited; 0, property not exhibited.
Modified from Muir WW III, Sams RA. Pharmacology and pharmacokinetics of antiarrhythmic drugs. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, pp 309–333.

dogs.[94, 95] Alterations in liver blood flow due to physiologic variables (e.g., feeding), disease states (e.g., cardiac failure), or concomitant administration of drugs affecting cardiac output or liver blood flow would be expected to affect the clearance of propranolol. Feeding increases (52 percent) the clearance of intravenous propranolol; this is mostly due to an increase in hepatic blood flow, which remains elevated for 5 to 7 hours after feeding.[96] Furthermore, propranolol decreases liver blood flow and decreases its own clearance as well as the clearance of other highly extracted drugs (e.g., lidocaine).[71]

The dose of propranolol required to suppress catecholamine-induced arrhythmias is 0.1 to 1.0 mg/kg IV (doses above 0.3 mg/kg are considered high) and 2 to 4 mg/kg orally. Doses may be given two or three times daily. Feeding does not affect the extent of oral absorption of propranolol but significantly delays the rate of absorption, shifting the time of peak plasma concentration from about 60 to 158 minutes after dosing.[96] Therapeutic plasma concentrations range from 40 to 85 ng/ml in humans and are probably similar in dogs and cats.

SIDE EFFECTS AND TOXICITY

Propranolol and other β-adrenoceptor-blocking drugs produce dose-dependent decreases in cardiac contractility and metabolic rate. Decreases in cardiac contractility and heart rate combine to produce decreases in stroke volume, cardiac output, arterial blood pressure, and myocardial oxygen consumption. These effects are particularly pronounced after intravenous administration and must be considered during oral therapy in patients with severe congestive heart failure or cardiomyopathy. Other important pharmacologic effects of propranolol are dependent on its nonselective β-adrenoceptor-blocking activity (see Table 17–7) and include decreases in renin release, bronchoconstriction, vasoconstriction, and inhibition of insulin release.[89]

Toxic concentrations of propranolol produce bradycardia, cardiac failure, and hypotension (see Table 17–6). Bronchospasm and hypoglycemia may occur but are rare. These effects can be prevented by the infusion of catecholamines (e.g., dopamine, dobutamine), which may precipitate cardiac rhythm disturbances. CNS depression and disorientation may occur during therapy with propranolol and other highly lipophilic β-adrenoceptor-blocking drugs. Propranolol markedly potentiates the depression of atrioventricular conduction produced by digitalis, calcium entry-blocking drugs, and Class Ia antiarrhythmics. The simultaneous administration of propranolol and a calcium entry-blocking drug (e.g., verapamil) can produce dramatic reductions in heart rate and cardiac contractility.

ATENOLOL

CLINICAL USE

Atenolol is a cardioselective β_1-adrenoceptor-blocking drug that is used as an alternative to propranolol in dogs and cats (see Tables 17–6, 17–7).[88] It may be preferred because of fewer side effects and less frequent dosing (0.2 to 0.5 mg/kg od to bid). Atenolol has been used successfully to reduce sinus rate, depress AV conduction, and eliminate premature ventricular depolarizations. The electrophysiologic and electrocardiographic effects of atenolol are similar to those of propranolol.

PHARMACOKINETICS

Atenolol has low lipophilicity and does not readily cross the blood-brain barrier, thereby decreasing the potential for CNS side effects. In contrast to propranolol-

lol, clearance is primarily renal rather than hepatic. Also, only approximately 10 percent of atenolol is bound to plasma proteins. The low lipophilicity of atenolol accounts for the difference in organ clearance. Likewise, low lipid solubility does not result in significant crossing of the blood-brain barrier, thereby decreasing the potential for CNS side effects (depression) more commonly seen with propranolol.

SIDE EFFECTS AND TOXICITY

Excessive doses of atenolol can cause bradycardia or AV nodal block. Although the frequency of lethargy and depression is much less with atenolol than with propranolol, these effects can still occur.

ESMOLOL

CLINICAL USE

Esmolol is an ultra-short-acting cardioselective β_1-adrenoceptor-blocking drug (see Tables 17–2, 17–6, 17–7).[15] Like that of other β-adrenoceptor-blocking agents, esmolol's antiarrhythmic activity is fully derived from β_1-blocking activity.[8, 24] Electrophysiologic, electrocardiographic, and hemodynamic effects are similar to those of other β-adrenoceptor-blocking drugs. Clinically, esmolol is effective therapy for sinus tachycardia, supraventricular tachycardia, and ventricular arrhythmias that are believed to be initiated or aggravated by increases in sympathetic tone. Esmolol is particularly effective as therapy for ventricular arrhythmias that are caused by drugs (thiobarbiturates, halothane) that sensitize the myocardium to arrhythmias.

PHARMACOKINETICS

Esmolol has a relatively short half-life (minutes) in dogs and cats. This drug is rapidly converted to inactive metabolites by blood esterase[97]; therefore, esmolol is given as either an intravenous bolus or a constant-rate infusion. Infusion rates ranging from 25 to 200 μg/kg/min have been used to successfully treat arrhythmias in dogs and cats; to reduce the pressure gradient, myocardial work, and myocardial oxygen consumption in dogs with aortic stenosis; and to reduce acutely or eliminate dynamic left ventricular outflow tract obstruction in cats with hypertrophic obstructive cardiomyopathy (Fox PR, personal communication). Like all β-adrenoceptor-blocking drugs, esmolol's effects are dependent upon prevailing sympathetic tone. Drug effects are more pronounced when sympathetic tone is high.

SIDE EFFECTS AND TOXICITY

As with other β-blockers, esmolol must be administered cautiously and under close supervision to patients in heart failure or that are volume depleted, in order to avoid the acute onset of hypotension, pulmonary congestion, and heart failure. Extravasation of esmolol from the vein can result in skin irritation because of its acidity. Furthermore, when used to treat life-threatening supraventricular arrhythmias, caution should be high if prior treatment with calcium channel blockers has been given. When these agents are combined, the potential for excessive bradycardia is increased.

AMIODARONE

CLINICAL USE

Although amiodarone is classified as a Class III antiarrhythmic (see Table 17–2), it actually possesses Class I, II, and IV activity as well.[98] It is an effective treatment for both supraventricular and ventricular arrhythmias in humans. In addition to its antiarrhythmic properties, it also possesses antifibrillatory activity. Today, use of amiodarone in veterinary patients is limited because of the cost and inadequate clinical studies to demonstrate effectiveness over side effects.

PHARMACOKINETICS

Amiodarone is a lipophilic weak base that has a large volume of distribution (2.22 L/kg).[99] It is cleared from the plasma (CL_p = 21.0 ± 7.0 ml/min/kg) by liver metabolism.[99] A major active metabolite, *N*-desmethylamiodarone, accumulates during chronic oral dosing. The concentration of amiodarone in the myocardium at steady-state plasma concentrations is almost 90 times its concentration in plasma, reflecting the selective uptake of the drug by heart tissues. Also, its lipid solubility is responsible for amiodarone's high concentrations in the liver and lungs. Furthermore, myocardial concentrations of the drug decrease much more slowly than plasma concentrations. The onset of action of orally administered amiodarone is slow and therefore requires loading doses.[100] Amiodarone is excreted by the luminal glands, skin, and biliary tract. Serum digoxin concentrations increase during concurrent amiodarone administration due to decreases in renal clearance of digoxin. This could predispose to signs and symptoms of digitalis toxicity. Oral bioavailability is poor, probably due to extensive first-pass metabolism. The complex pharmacokinetics of amiodarone result in difficult dosing schedules and ill-defined therapeutic plasma considerations.

ELECTROPHYSIOLOGY AND ELECTROCARDIOGRAPHY

Amiodarone was initially introduced as a coronary artery vasodilator.[83] However, it markedly prolongs the action potential duration and effective refractory period in both atrial and ventricular tissues. Therapeutic doses of amiodarone decrease sinus rate and depress AV conduction velocity. The ECG usually demonstrates a slowing of sinus rate, PR and QT prolongation, and a flattening of the T wave (see Table 17–5). Cardiac contractility and arterial blood pressure are minimally depressed by therapeutic doses of amiodarone.

SIDE EFFECTS AND TOXICITY

Serious side effects can occur with amiodarone (see Table 17–6) as reported in humans.[100, 101] Pulmonary fibrosis, gray-bluish discoloration of the skin, corneal microdeposits, and altered thyroid function can develop. Moreover, although amiodarone when used alone does not usually cause torsades de pointes, it is more likely when combined with some other drugs (i.e., Class I antiarrhythmics). Until recently, the use of amiodarone in humans was considered only for the most severe arrhythmias. However, with much lower doses and the demonstration that amiodarone effectively lowered morbidity and mortality, it has become more generally used.[100] The extreme effectiveness of amiodarone as therapy for potentially lethal cardiac arrhythmias that are refractory to conventional antiarrhythmic therapy warrants its continued investigation in dogs with atrial and ventricular arrhythmias despite the potential for toxicity.

BRETYLIUM

CLINICAL USE

Bretylium, a Class III antiarrhythmic (see Table 17–2), has had limited use in clinical veterinary medicine. It was initially introduced as a chemical antifibrillatory drug. However, this action was not appreciated until it was learned that adequate tissue concentrations in the heart did not occur until several hours after intravenous administration. The use of bretylium is probably limited to situations of impending ventricular fibrillation in an intensive care situation.

PHARMACOKINETICS

Bretylium is a hydrophilic quaternary amine (i.e., it is ionized at all pH values). The rate and extent of tissue distribution are less, and therefore its volume of distribution is lower than that of other drugs discussed in this chapter because of its greater polarity. The total clearance of bretylium is low and is attributed to renal elimination.[101] Total clearance is diminished in those patients with renal dysfunction, and the dose should be reduced accordingly. The limited volume of distribution and low clearance result in a comparatively long half-life of about 10.4 hours. Bretylium is well absorbed after intramuscular administration but is not absorbed after oral administration.

Antifibrillatory effects are related more closely to tissue drug concentration than to plasma drug concentration. Drug concentrations in plasma decline rapidly after intravenous dosing; tissue concentrations rise slowly, peaking at 1.5 to 6 hours.[102] Therefore, antifibrillatory effects should not be expected immediately after IV dosing but are delayed for 3 to 6 hours after a single dose. Intravenous doses of 2 to 6 mg/kg in dogs produce myocardial tissue concentrations that peak at 6 to 15 μg/ml in 3 to 6 hours. These concentrations increase ventricular fibrillation thresholds 5- to 18-fold in dogs with or without myocardial ischemia.

ELECTROPHYSIOLOGY AND ELECTROCARDIOGRAPHY

Bretylium produces antiarrhythmic effects by both indirect and direct actions (see Table 17–3). Bretylium therapy results in an initial release of catecholamines from adrenergic nerve terminals. This effect is transient and is followed by a prolonged period during which norepinephrine release from postganglionic nerve terminals is inhibited. The direct actions of bretylium are limited to ventricular muscle and Purkinje tissues, in which it markedly prolongs action potential duration and the effective refractory period.[103–105] Bretylium increases the threshold necessary to induce ventricular fibrillation.[103, 104] Clinically, administration of bretylium in therapeutic dosages causes a transient increase in sinus and AV conduction velocity, presumably associated with initial catecholamine release.[83] This is followed by a longer period during which heart rate and AV conduction are depressed. The ECG is not significantly changed by bretylium.

SIDE EFFECTS AND TOXICITY

Toxicity associated with bretylium therapy is rare. Hypotension is infrequent and, when it does occur, is easily treated with intravenous fluids. Ataxia, nausea, and vomiting may occur after rapid intravenous administration. No significant drug interactions have been reported in conjunction with bretylium therapy. Bretylium should not be administered to extremely bradycardic or hypotensive animals.

SOTALOL

CLINICAL USE

Sotalol is a Class III antiarrhythmic and β-blocker that has been available for clinical use in Europe and

South America for over 30 years (see Table 17–2).[23, 24] It has been used to treat both ventricular and supraventricular arrhythmias.

PHARMACOKINETICS

Sotalol is almost 100 percent bioavailable in dogs and cats, with plasma concentrations reaching their maximum within 1.5 to 2 hours after oral administration.[23] Sotalol demonstrates a relatively longer half-life than most antiarrhythmic drugs do and is eliminated in the urine and feces. Absorption of sotalol from the gastrointestinal tract is delayed by meals containing calcium, and drug elimination is markedly prolonged in patients with renal disease. Oral dosages of sotalol in the dog range from 3 to 5 mg/kg administered two or three times daily. The lowest effective dose should be used to decrease the incidence of side effects.

ELECTROPHYSIOLOGY AND ELECTROCARDIOGRAPHY

Efficacy in humans for treatment of supraventricular and ventricular arrhythmias has been established and extensively studied. A major factor in its efficacy is the combined Class III and Class II actions present in the racemic form of sotalol (d,l sotalol). When only the Class III action (d sotalol) is available, the beneficial effect for decreasing mortality in humans is lost. Sotalol prolongs the ventricular action potential duration and thereby potentially produces antifibrillatory activity[7]; it also inhibits the time-dependent potassium current (delayed rectifier, I_K). Minimal depressant effects are observed on the background potassium current (inward rectifier, I_K). These actions produce a marked prolongation of action potential duration and refractoriness and are most pronounced in Purkinje fibers, although significant prolongation of both atrial and ventricular myocyte action potentials also occurs.

Therapeutic concentrations of sotalol do not affect the maximum rate of rise of the cardiac action potential (phase 0) nor do they modify the rate of phase 4 diastolic depolarization in sinoatrial, atrioventricular, or other automatic cells.[23] Sinus rate in intact animals is often decreased, however, due to sotalol's nonselective β-blocking activity (see Table 17–5). Unlike other β-blockers (propranolol, atenolol) without intrinsic sympathomimetic activity (pindolol), sotalol has the potential to produce a positive inotropic effect by prolonging action potential duration and increasing the magnitude of the inward calcium current. The clinical significance of this activity is controversial and may be overshadowed by nonselective β-blocking properties. This latter point is supported by the observation that intravenous and oral administration of sotalol to dogs decreases heart rate, stroke volume, ejection fraction, cardiac output, and dP/dt (a load-dependent index of ventricular contractility).

SIDE EFFECTS AND TOXICITY

Adverse effects associated with sotalol administration include hypotension, bradyarrhythmias, depression, nausea, vomiting, and diarrhea (see Table 17–6).[23] Congestive heart failure may be precipitated in animals with preexisting cardiac disease. As with other Class III and Class Ia and Ic antiarrhythmics, sotalol has the potential to produce proarrhythmic effects, including the development of torsades de pointes, particularly in hypokalemic patients or patients receiving relatively high doses of loop diuretics (furosemide).[6, 46, 61] In humans, torsades de pointes is more common with sotalol than with amiodarone.

VERAPAMIL AND DILTIAZEM

CLINICAL USE

Verapamil and diltiazem are examples of Class IV antiarrhythmic agents (see Table 17–2) that can be effectively used to treat supraventricular arrhythmias. Both result in some arteriolar dilation, although vascular selectivity is substantially less than in dihydropyramidines (i.e., nifedipine, amlodipine). Each drug can be given parenterally or orally as an antiarrhythmic (for specifics with regard to use, see chapter 18).

PHARMACOKINETICS

Verapamil is a lipophilic weak base that is rapidly and extensively distributed to extravascular tissues. Total body clearance is very high due to extensive liver metabolism and possibly other routes of elimination.[106] Two metabolites resulting from successive demethylation are found in plasma after oral and intravenous dosing and may contribute to the drug's pharmacologic effect.[106] The oral bioavailability of verapamil is low due to extensive first-pass metabolism, but the metabolite, nonverapamil, is active in humans. Verapamil is extensively protein bound. Diltiazem also is highly protein bound, but has less first-pass hepatic metabolism than verapamil. Diltiazem is only partially excreted by the kidneys and primarily eliminated in the gastrointestinal tract. Unless the slow-release formulations of diltiazem are used, dosing must be frequent (three to five times daily in the dog). Because of metabolite accumulation, this dosing interval may decrease with chronic use.

Verapamil decreases the renal clearance of digoxin, resulting in increased serum digoxin concentrations.[107, 108] Diltiazem does not interfere with dosing requirements for digoxin.

ELECTROPHYSIOLOGY AND ELECTROCARDIOGRAPHY

Class IV antiarrhythmic drugs derive their electrophysiologic and antiarrhythmic activity by producing dose-dependent depression of transmembrane calcium flux through the slow L-type calcium channel.[109] This action has led to the terms "slow-channel inhibitory drugs," "calcium antagonists," and "calcium-entry blockers" (the last of which is preferred). Although a wide variety of compounds have been developed that inhibit calcium entry into cardiac cells, only verapamil and diltiazem demonstrate significant antiarrhythmic activity.[109] This action is believed to be due to their ability to depress the slow inward Ca^{++} current and minimally to inhibition of the fast Na^{+} current. Because of dose-dependent decreases in sinus rate and atrioventricular conduction velocity, slowing of the sinus rate and PR interval prolongation can be documented (see Tables 17–3, 17–6).

SIDE EFFECTS AND TOXICITY

Verapamil and diltiazem can cause decreases in cardiac contractility, vasodilation, and hypotension (see Table 17–6).[26, 109] Depression, anorexia, and lethargy can be seen with these calcium-entry blockers.

Toxic doses of verapamil or diltiazem can produce sinus bradycardia, AV block, hypotension, and heart failure.[25] These deleterious effects can be antagonized by the intravenous administration of calcium-containing solutions or catecholamines.

DIGITALIS GLYCOSIDES

CLINICAL USE

Digoxin is the most common digitalis glycoside used to treat supraventricular arrhythmias. Atrial fibrillation is the most frequent supraventricular arrhythmia treated in dogs with digoxin (for specifics regarding treatment see chapter 18).

PHARMACOKINETICS

Digoxin has a low therapeutic to toxic ratio. In years past, excessive doses of digoxin resulted in frequent toxicity. Currently, more conservative and cautious dosing, knowledge of drug and disease interactions, and monitoring of plasma digoxin concentrations facilitate therapy with less toxicity. Digoxin is excreted primarily through the kidneys and, therefore, in renal failure, the dose must be decreased. Renal excretion of digoxin is also reduced during hypokalemia.

ELECTROPHYSIOLOGY AND ELECTROCARDIOGRAPHY

Digitalis glycosides produce indirect and direct antiarrhythmic effects.[110] Most of the indirect antiarrhythmic actions are due to increases in parasympathetic tone and sympathetic inhibition (see Table 17–3). Digitalis glycosides decrease sinus rate, depress AV conduction velocity, prolong AV refractoriness, enhance intra-atrial conduction, and depress atrial specialized-fiber automaticity. Digitalis derives its positive inotropic effects by producing dose-dependent inhibition of the Na^{+}, K^{+}-ATPase-dependent pump.[110] Inhibition of the Na^{+}, K^{+} pump results in the accumulation of intracellular sodium that exchanges for extracellular calcium, thereby increasing intracellular calcium concentration, which ultimately produces a more forceful cardiac contraction. Digitalis-induced increase in inotropy, decrease in cardiac size, and increase in myocardial perfusion may be partially responsible for improved intra-atrial conduction and the abolition of ventricular arrhythmias. Prolongation of the PR interval, although inconsistent, is the most frequent ECG change observed during digitalis therapy.

SIDE EFFECTS AND TOXICITY

Toxic doses of digitalis cause cellular depolarization and marked slowing of conduction in atrial and ventricular specialized fibers and the AV node. These actions can produce a wide variety of conduction disturbances, including first-, second-, and potentially third-degree AV block; right or left bundle branch block; and reentrant atrial or ventricular arrhythmias. The excessive accumulation of intracellular calcium can result in abnormalities in intracellular calcium kinetics, causing oscillation of the resting membrane potential, delayed afterdepolarizations (DADs), and the development of atrial and ventricular arrhythmias. More common toxic side effects include depression, restlessness, nausea, vomiting, anorexia, and diarrhea (see Table 17–6).

Digitalis toxicity can be managed by decreasing or withdrawing digitalis therapy. Lidocaine and phenytoin are particularly effective for treating digitalis-induced arrhythmias. The simultaneous administration of digoxin with certain drugs (e.g., furosemide, quinidine, propafenone, amiodarone, and verapamil) can decrease the renal clearance of digoxin, increase digoxin serum concentrations, and potentially induce digitalis toxicity.[110] Hypokalemia decreases digoxin binding to skeletal muscle, increasing serum digoxin plasma concentrations and predisposing to digitalis toxicity.

POTASSIUM AND MAGNESIUM

Throughout this discussion, continued reference has been made to maintaining normal serum potassium

concentrations. Indeed, it can be unequivocally stated that increases or decreases in serum potassium concentration can be responsible for the development of certain cardiac arrhythmias.[87, 111, 112] *Hyperkalemia* produces sinus bradycardia, first-, second-, and third-degree atrioventricular block, sinoventricular rhythm disturbances, sinoventricular rhythms, and ultimately, widening of the QRS complex, poor ventricular function, cardiac failure, and ventricular fibrillation. *Hypokalemia* produces persistent nonresponse and supraventricular tachycardia and predisposes to ventricular fibrillation. Abnormalities in serum potassium concentration can have dramatic effects upon antiarrhythmic therapy and the effects of antiarrhythmic drugs. Indeed, most antiarrhythmic drugs are ineffective during hypokalemia and potentially toxic during hyperkalemia. Furthermore, many antiarrhythmic drugs with the potential to produce proarrhythmic effects are more likely to do so in hypokalemic patients. Relatively minor proarrhythmic effects in normokalemic patients can transform into severe polymorphic ventricular tachycardia (including torsades de pointes) in states of hypokalemia.[34, 46, 61] Therefore, serum potassium concentrations should be monitored during initiation of antiarrhythmic therapy if hypokalemia is suspected, or during administration of large doses of loop diuretics.

Magnesium deficiency is associated with chronic cardiovascular disease and, either by itself or in association with hypokalemia, has been demonstrated to produce a variety of cardiac arrhythmias, particularly ventricular tachycardias.[36, 112, 113] Magnesium is necessary for normal Na^+, K^+-ATPase pump function and exerts control over intracellular potassium homeostasis. Magnesium is also required for protein and nucleic acid synthesis within cells and in the mitochondria. Magnesium homeostasis is important for normal function of potassium channels in cardiac myocytes and therefore can influence action potential, duration, and resting membrane potential.

Magnesium is recognized as a physiologic calcium channel blocker that may interfere with calcium currents, causing shortening of the action potential duration. Decreases in magnesium can in fact shorten action potential amplitude and duration and decrease

TABLE 17–8
Examples of Drug-Drug Interactions Involving Antiarrhythmic Drugs

Class	Drug	Interaction with	Result
Ia	Quinidine	Digoxin	Increased digoxin level
		Other Class I antiarrhythmics	Added negative inotropic effect and/or depressed conduction
		β-blockers, calcium antagonists	Enhanced hypotension, negative inotropic effect
		Amiodarone	Increased risk of torsades de pointes
		Varapamil	If hypokalemia, risk of torsades de pointes
		Diuretics	Increased quinidine level
	Procainamide	Few interactions	
		Captopril	Possible immune effects
Ib	Lidocaine	β-blockers, cimetidine, halothane	Reduced hepatic clearance of lidocaine; toxicity
	Phenytoin	Chloramphenicol	Reduced hepatic clearance of phenytoin; long half-life
	Tocainide	Few interactions	
	Mexiletine	Few interactions	
Ic	Propafenone	Drugs inhibiting SA or AV nodes (β-blockers, verapamil, diltiazem, digoxin)	SA and AV nodal depression
		Drugs with negative inotropic effects	Depressed myocardium
		Drugs with depressed HV conduction (quinidine, procainamide)	Conduction delay
		Digoxin	Digoxin level increased
II	Propranolol (β-blockers)	Anesthetics	Myocardial depression
		Lidocaine	Reduced clearance
III	Amiodarone	Class Ia drugs	Risk of torsades de pointes
		Digoxin	Digoxin level increased
		Flecainide	Flecainide level increased
	Sotalol	Diuretics, Class Ia agents, amiodarone, phenothiazines	Risk of torsades de pointes
IV	Verapamil	β-blockers	Myocardial depressants
		Digoxin, quinidine	Increased digoxin concentration
	Diltiazem	β-blockers	Myocardial depression

Modified from Marcus FI, Opie LH. Antiarrhythmic agents. *In* Opie LH (ed): Drugs for the Heart. 3rd ed. Philadelphia, WB Saunders, 1991, p 189.

resting membrane potential; this can predispose to spontaneous automaticity, decreases in cardiac refractoriness, and development of tachyarrhythmias.[113] Increases in magnesium produce negative chronotropic and antiarrhythmic effects. Intravenous magnesium administration produces slowing of the heart rate, minimal prolongation of the PR interval, and mild systemic hypotension. Ideally, serum magnesium concentrations should be evaluated in dogs and cats with chronic heart disease or in animals receiving high doses of loop diuretics (e.g., furosemide), particularly since hypomagnesemia can produce ventricular arrhythmias.[113] In states of hypomagnesemia, the administration of magnesium chloride (0.3 mEq/kg) over 10 minutes followed by a constant-rate infusion of 0.2 mEq/kg/hr can be used to return serum magnesium concentrations to within normal limits (1.5 to 2.4 mEq/L).

DRUG-DRUG AND DRUG-DISEASE INTERACTIONS

Interactions between drugs (Table 17–8) or between drugs and various disease states are common. When severe, they can alter drug concentrations in the blood and, therefore, at the drug-receptor site to such an extent that therapeutic failure may result. Although a given drug dose may result in clinical efficacy when administered, the same drug may produce toxicity or be ineffective if its pharmacokinetics are altered by the administration of another drug or by a disease process. Examples of pharmacokinetic parameters that may be altered from drug-drug interactions are illustrated in Table 17–8.

REFERENCES

1. Allessie MA, Konings K, Kirchhof CJHJ, et al. Electrophysiologic mechanisms of perpetuation of atrial fibrillation. Am J Cardiol 77:10A, 1996
2. Hondeghem LM, Katzung BG. Mechanism of action of antiarrhythmic drugs. *In* Sperelakis N (ed): Physiology and Pathophysiology of the Heart. 3rd ed. Boston, Kluwer Academic Publishers, 1995, p 589
3. Link M, Homoud M, Foote CB, et al. Antiarrhythmic drug therapy for ventricular arrhythmias: current perspectives. J Cardiovasc Electrophysiol 7:653, 1996
4. Kadish A, Morady F. Mechanism-specific therapy of ventricular tachycardia. J Cardiovasc Electrophys 1:68, 1990
5. Binah O, Rosen MR. Mechanism of ventricular arrhythmias. Circulation 85 (Suppl I):125, 1992
6. Singh BN. Do antiarrhythmic drugs work? Some reflections on the implications of the cardiac arrhythmia suppression trial. Clin Cardiol 13:725, 1990
7. Woosley RL. New concepts affecting the use of antiarrhythmic agents. Cardiovasc Drugs Ther 4:541, 1990
8. Camm AJ. Current antiarrhythmic therapy overview. Cardiovasc Drugs Ther 4:531, 1990
9. Vaughan-Williams EM. Classification of antiarrhythmic drugs. *In* Sandoe E, Flensted-Jensen E, Olesen K (eds): Cardiac Arrhythmias. Astra, Sweden, Sodertalje, 1970, p 449
10. Singh BN, Vaughan-Williams EM. A third class of antiarrhythmic action. Effects on atrial and ventricular intracellular potentials, and other pharmacological actions on cardiac muscle of MJ 1999 and AH 3474. Br J Pharmacol 39:675, 1970
11. Singh BN, Vaughan-Williams EM. A fourth class of antidysrhythmic action? Effect of verapamil on ouabain toxicity, on atrial and ventricular intracellular potentials, and other features of cardiac function. Cardiovasc Res 6:109, 1972
12. Williams EMV: A classification of antiarrhythmic actions reassessed after a decade of new drugs. J Clin Pharmacol 24:129, 1984
13. Harrison DC. Antiarrhythmic drug classification: new science and practical applications. Am J Cardiol 56:185, 1985
14. The Task Force of the Working Group on Arrhythmias of the European Society of Cardiology: the "Sicilian Gambit." Eur Heart J 12:1112, 1991
15. Members of the Sicilian Gambit. Antiarrhythmic Therapy: A pathophysiologic Approach. Armonk, NY, Futura Publishing Company, 1994
16. Maze M, Smith GM. Identification of receptor mechanism mediating epinephrine-induced arrhythmias during halothane anesthesia in the dog. Anesthesiology 59:322, 1983
17. Penkoske PA, Sobel SE, Corr PB. Disparate electrophysiological alterations accompanying dysrhythmia due to coronary occlusion and reperfusion in the cat. Circulation 58:1023, 1978
18. Muir WW, Sams R. Clinical pharmacodynamics and pharmacokinetics of β-adrenoceptor blocking drugs in veterinary medicine. Comp Cont Ed 6:156, 1984
19. Cardinal R, Sasyniuk BI. Electrophysiological effects of bretylium tosylate on subendocardial Purkinje fibers from infarcted canine hearts. J Pharmacol Expl Ther 204:159, 1978
20. Lucchesi BR, Chi L, Friedrichs GS, et al. Antiarrhythmic versus antifibrillatory actions: inference from experimental studies. Am J Cardiol 72:25F, 1993
21. Singh BN. The coming age of the class III antiarrhythmic principle: retrospective and future trends. Am J Cardiol 78(4A):17, 1996
22. Lazzara R. From first class to third class: recent upheaval in antiarrhythmic therapy—lessons from clinical trials. Am J Cardiol 78(4A):28, 1996
23. Ruffy R. Sotalol. J Cardiovasc Electrophys 4:89, 1993
24. Opie LH, Frishman WH, Thadani U. Calcium channel antagonists (calcium entry blockers). *In* Opie LH (ed): Drugs for the Heart. 4th ed. Philadelphia, WB Saunders, 1995
25. Antman EM, Stone PH, Muller JE, Braunwald E. Calcium channel blocking agents in the treatment of cardiovascular disorders. Part 1. Basic and clinical electrophysiologic effects. Ann Intern Med 93:875, 1980
26. Stone PH, Antman EM, Muller JE, Braunwald E. Calcium channel blocking agents in the treatment of cardiovascular disorders. Part II. Hemodynamic effects and clinical applications. Ann Intern Med 93:886, 1980
27. Singh BN, Baky S, Nademanee K. Second-generation calcium antagonists: search for greater selectivity and versatility. Am J Cardiol 55:214B, 1985

28. Pelliccia F, Cianfrocca C, Romeo F, Peale A. Hypertrophic cardiomyopathy: long-term effects of propranolol versus verapamil in preventing sudden death in "low-risk" patients. Cardiovasc Drugs Ther 4:1515, 1990
29. Setaro JF, Zanet BL, Schulman DS, et al. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. Am J Cardiol 66:981, 1990
30. Bright JM, Golden AL, Gompf RE, et al. Evaluation of the calcium channel-blocking agents diltiazem and verapamil for treatment of feline hypertrophic cardiomyopathy. J Vet Intern Med 5:272, 1991
31. Spedding M, Paoletti R. Classification of calcium channels and calcium antagonists. Progress report. Cardiovasc Drugs Ther 6:35, 1992
32. Frishman WH, Sonnenblick EH. Calcium channel blockers. *In* Schlant RC, Alexander RW (eds): The Heart, Arteries, and Veins. New York, McGraw-Hill, 1994, p 1291
33. Nattel S, Bailey JC. Time course of the electrophysiological effects of quinidine on canine cardiac Purkinje fibers: concentration dependence and comparison with lidocaine and disopyramide. J Pharmacol Exp Ther 225:176, 1983
34. Materson BJ, Caralis PV. Risk of cardiac arrhythmias in relation to potassium imbalance. J Cardiovasc Pharmacol 6:S493, 1984
35. Giardina EGV, Lipka LJ. Class Ia antiarrhythmic agents: quinidine, procainamide, disopyramide. *In* Podrid PJ, Kovey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis and Management. Baltimore, Williams and Wilkins, 1995, p 369
36. McGovern B. Hypokalemia and cardiac arrhythmias. Editorial views. Anesthesiology 63:127, 1985
37. Chassaing C, Duchene-Marullaz P, Paire M. Mechanism of action of quinidine on heart rate in the dog. J Pharmacol Exp Ther 222:688, 1982
38. Goette A, Honeycutt C, Langberg JJ. Electrical remodeling in atrial fibrillation. Circulation 94:2968, 1996
39. Neff CA, Davis LE, Baggot JD. A comparative study of the pharmacokinetics of quinidine. Am J Vet Res 33:1521, 1972
40. Hiatt E, Quinn G. The distribution of quinine, quinidine, cinchonine, and cinchonidine in fluids and tissues of dogs. J Pharmacol Exp Ther 83:101, 1985
41. Mayersohn M, Perrier D, Fenster P, Marcus FI. Steady-state plasma concentrations of quinidine and propranolol. Clin Pharmacol Ther 97:678, 1979
42. Leahey EB, Bigger JT, Butler VP Jr. Quinidine-digoxin interaction. Time course and pharmacokinetics. Am J Cardiol 48:1141, 1981
43. Warner NJ, Leahey EB Jr, Hougen JJ, et al. Tissue digoxin concentrations during the quinidine-digoxin interaction. Am J Cardiol 51:1717, 1983
44. Lathers GM, Roberts J. Are the sympathetic neural effects of digoxin and quinidine involved in their action of cardiac rhythm? J Cardiovasc Pharm 7:350, 1985
45. Schmid PG, Nelson LD, Mark AL, et al. Inhibition of adrenergic vasoconstriction by quinidine. J Pharmacol Exp Ther 188:124, 1974
46. Zipes DP. Proarrhythmic effects of antiarrhythmic drugs. Am J Cardiol 59:26E, 1987
47. Roden DH, Hoffman BF. Action potential, prolongation, and induction of abnormal automaticity by low quinidine concentrations in canine Purkinje fibers. Relationship to potassium and cycle length. Circ Res 56:857, 1985
48. Jaillon P, Winkle RA. Electrophysiologic comparative study of procainamide and *N*-acetylprocainamide in anesthetized dogs: concentration-response relationships. Circulation 60:1286, 1979
49. Rosen MR, Merker C, Gelband H, Hoffman BF. Effects of procainamide on the electrophysiologic properties of the canine ventricular conducting system. J Pharmacol Exp Ther 195:438, 1973
50. Papich MG, Davis LE, Davis CA, et al. Pharmacokinetics of procainamide hydrochloride in dogs. Am J Vet Res 47:2351, 1986
51. Bagwell EE, Walle J, Drayer DE, et al. Correlation of the electrophysiological and antiarrhythmic properties of the *N*-acetyl metabolite of procainamide with plasma and tissue concentrations in the dog. J Pharmacol Exp Ther 197:38, 1976
52. Badke FR, Walsh RA, Crawford MH, et al. Hemodynamic effects of *N*-acetyl procainamide compared with procainamide in conscious dogs. Circulation 6:1142, 1981
53. Bigger JT, Hoffman BF. Antiarrhythmic drugs. *In* Gilman AG, Goodman LS, Rall TW, Murad F (eds): The Pharmacological Basis of Therapeutics. 7th ed. New York, Macmillan, 1985, p 748
54. Heel RC, Brogden RN, Speight TM, Avery GS. Disopyramide: a review of its pharmacological properties and therapeutic use in treating cardiac arrhythmias. Drugs 15:331, 1978
55. Ranney RE, Dean RR, Karim A, Radzialowski FM. Disopyramide phosphate: pharmacokinetic and pharmacologic relationships of a new antiarrhythmic agent. Arch Int Pharmacodyn 191:162, 1971
56. Kus T, Sasyniuk B. Electrophysiological actions of disopyramide phosphate on canine ventricular muscle and Purkinje fibers. Circ Res 37:844, 1975
57. Karim A, Cook C, Novotney RI, et al. Pharmacokinetics and steady-state myocardial uptake of disopyramide in the dog. Drug Metab Dispos 6:338, 1978
58. Cook CS, Karim A, Sollman P. Stereoselectivity in the metabolism of disopyramide enantiomers in rat and dog. Drug Metab Dispos 10:116, 1982
59. Yeh BK, Sung P, Scherlag BJ. Effects of disopyramide on electrophysiological and mechanical properties of the heart. J Pharm Sci 62:1924, 1973
60. Walsh RA, Horwitz LD. Adverse hemodynamic effects of intravenous disopyramide compared with quinidine in conscious dogs. Circulation 60:1053, 1979
61. Bigger JT, Sahar DI. Clinical types of proarrhythmic response to antiarrhythmic drugs. Am J Cardiol 59:2E, 1987
62. Feely J, Wade D, McAllister CB. Effect of hypotension on liver blood flow and lidocaine disposition. N Engl J Med 307:866, 1982
63. Campbell RWF. Class Ib antiarrhythmic agents. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis and Management. Baltimore, Williams and Wilkins, 1995, p 391
64. Hondeghem LM, Grant AO, Jensen RA. Antiarrhythmic drug action: selective depression of hypoxic cardiac cells. Am Heart J 87:602, 1974
65. Roos JC, Dunning AJ. Effects of lidocaine on impulse formation and conduction defects in man. Am Heart J 89:686, 1975
66. Harrison DC, Alderman EI. The pharmacology and clinical use of lidocaine as an antiarrhythmic drug. Modern Treat 9:139, 1972
67. Keenhagan JB, Boyes RN. The tissue distribution, metabolism, and excretion of lidocaine in rats, guinea

pigs, dogs and man. J Pharmacol Exp Ther 180:454, 1972
68. Wilcke JR, Davis LE, Neff-Davis CA, Koritz CD. Pharmacokinetics of lidocaine and its active metabolites in dogs. J Vet Pharmacol Ther 6:49, 1983
69. Branch RA, Shand DG, Wilkinson CR, Nies AS. The reduction of lidocaine clearance by dl-propranolol: An example of hemodynamic drug interaction. J Pharmacol Exp Ther 184:515, 1973
70. Branch RA, Shand DC, Wilkinson GR, Nies AS. The reduction of lidocaine clearance by dl-propranolol. N Engl J Med 303:373, 1980
71. Lineberger AS, Sprague DH, Battaglini JW. Sinus arrest associated with cimetidine. Anesth Analg 64:554, 1985
72. Wilcke JR, Davis LE, Neff-Davis CA. Determination of lidocaine concentrations producing therapeutic and toxic effects in dogs. J Vet Pharmacol Ther 6:105, 1983
73. Mason DT, DeMaria AN, Amsterdam EA, et al. Antiarrhythmic agents. I: Mechanisms of action and clinical pharmacology. Drugs 5:261, 1973
74. Mason DT, DeMaria AN, Amsterdam EA, et al. Antiarrhythmic agents. II: therapeutic considerations. Drugs 5:292, 1973
75. Ikeda M, Dohi T, Tsujimoto A. Inhibition of γ-aminobutyric acid release from synaptosomes by local anesthetics. Am Soc Anesth 38:495, 1983
76. Calvert CA, Pickus CW, Jacobs CJ. Efficacy and toxicity of tocainide for the treatment of ventricular tachyarrhythmias in Doberman pinschers with occult cardiomyopathy. J Vet Intern Med 10:235, 1996
77. Berlin-Wahlen A, Barcus JC, Keenhagen JB, et al. Elimination of *N*-(2-aminoacyl)-2,6-xylidines after intravenous infusion in dogs. Acta Pharm Suec 14:417, 1977
78. Coltart DJ, Berndt TB, Kernoff R, Harrison DC. Antiarrhythmic and circulatory effects of Astra W36095—a new lidocaine-like agent. Am J Cardiol 34:35, 1974
79. Campbell NPS, Kelly JG, Adgey AAJ, Shanks RG. The clinical pharmacology of mexiletine. Br J Clin Pharmacol 6:103, 1978
80. Singh S, Klein R, Eisenberg B, et al. Long-term effect of mexiletine on left ventricular function and relation to suppression of ventricular arrhythmia. Am J Cardiol 66:1222, 1990
81. Podrid PJ, Kowery PR, Frishman WH, et al. Comparative cost-effectiveness analysis of quinidine, procainamide, and mexiletine. Am J Cardiol 68:1662, 1991
82. Duff HJ, Rahmberg M, Sheldon RS. Role of quinidine in the mexiletine-quinidine interaction: electrophysiologic correlates of enhanced antiarrhythmic efficacy. J Cardiovasc Pharmacol 16:685, 1990
83. Lucchesi BR, Patterson ES. Antiarrhythmic drugs. *In* Antonaccio MJ (ed): Cardiovascular Pharmacology. 2nd ed. New York, Raven Press, 1984, p 329
84. Prescott LF, Pottage A, Clements JA. Absorption, distribution and elimination of mexiletine. Postgrad Med J 53:50, 1977
85. Beckett AH, Chidomere EC. The distribution and excretion of mexiletine in man. Postgrad Med J 53:60, 1977
86. Pratt CM. Class Ic antiarrhythmic agents: propafenone, flecainide, and ethrozine. *In* Podrid PJ, Kowery PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis and Management. Baltimore, Williams and Wilkins, 1995, p 391
87. The ESVEM Investigators. The ESVEM trial: electrophysiologic study versus electrocardiographic monitoring for selection of antiarrhythmic therapy of ventricular tachyarrhythmias. Circulation 79:1354, 1989
88. Muir WW, Sams RA. Clinical pharmacodynamics and pharmacokinetics of β-adrenoceptor blocking drugs in veterinary medicine. Comp Cont Ed 156:156, 1984
89. Shiroff RA, Mathis J, Zellis R, et al. Propranolol rebound: a retrospective study. Am J Cardiol 41:778, 1978
90. Evans GH, Nies AS, Shand DG. The disposition of propranolol. III. Decreased half-life and volume of distribution as a result of plasma binding in man, monkey, dog and rat. J Pharmacol Exp Ther 186:114, 1973
91. Vu VT, Abramson FP. The pathways of propranolol metabolism in dog and rat liver—10,000 g supernatant fractions. Drug Metab Dispos 8:300, 1980
92. Walle T, Oatis JE, Walle UK, Knapp DR. New ring hydroxylated metabolites of propranolol. Drug Metab Dispos 10:122, 1982
93. Fitzgerald JD, O'Donnell SR. Pharmacology of 4-hydroxypropranolol, a metabolite of propranolol. Br J Pharmacol 43:222, 1971
94. Orme CF, Orme ML, Buranapong P, et al. Contribution of the liver to the overall elimination of propranolol. J Pharmacokinet Biopharm 4:17, 1976
95. Kates RE, Keene BW, Hamlin RL. Pharmacokinetics of propranolol in the dog. J Vet Pharmacol Ther 2:21, 1979
96. Bai SA, Walle UK, Walle T. Influence of food on the intravenous and oral dose kinetics of propranolol in the dog. J Pharmacokinet Biopharm 13:229, 1985
97. Opie LH, Sonnenblick EH, Frishman W, Thadani U. Beta-blocking agents. *In* Opie LH (ed): Drugs for the Heart. Philadelphia, WB Saunders, 1995, p 1
98. Swan JH, Chisholm AW. Control of recurrent supraventricular tachycardia with amiodarone hydrochloride. Can Med Assoc J 114:43, 1976
99. Latini R, Connolly SJ, Kates RE. Myocardial disposition of amiodarone in the dog. J Pharmacol Exp Ther 224:603, 1983
100. Marcus FI, Opie LH. Antiarrhythmic agents. *In* Opie LH (ed): Drugs for the Heart. Philadelphia, WB Saunders, 1995, p 207
101. Naccarelli GV, Dougherty AH. Amiodarone: a review of its pharmacologic, antiarrhythmic, and adverse effects. *In* Podrid PJ, Kowery PR (eds): Cardiac Arrhythmias: Mechanisms, Diagnosis and Management. Baltimore, Williams and Wilkins, 1995, p 434
102. Anderson JL, Patterson E, Conlon M, et al. Kinetics of antifibrillatory effects of bretylium: correlation with myocardial drug concentrations. Am J Cardiol 46:583, 1980
103. Bigger JT Jr, Jaffe CC. The effect of bretylium tosylate on the electrophysiologic properties of ventricular muscle and Purkinje fibers. Am J Cardiol 27:82, 1971
104. Sanna C, Arcidiacono R. Chemical ventricular defibrillation of the human heart with bretylium tosylate. Am J Cardiol 32:982, 1973
105. Breznock EM, Kagan K, Hibser NK. Effects of bretylium tosylate on the in vivo fibrillating canine ventricle. Am J Vet Res 38:89, 1977
106. McIlhenny HM. Metabolism of [^{14}C] verapamil. J Med Chem 14:1178, 1971
107. Klein HO, Kaplialinsky E. Verapamil and digoxin: their respective effects on atrial fibrillation and their interaction. Am J Cardiol 50:894, 1982
108. Kuhlman J. Effects of verapamil, diltiazem, and nifedipine on plasma levels and renal excretion of digitoxin. Clin Pharmacol Ther 38:667, 1985
109. Katz AM. Basic cellular mechanisms of action in the calcium-channel blockers. Am J Cardiol 55:2B, 1985
110. Hoffman BF, Bigger TJ. Digitalis and allied cardiac

glycosides. *In* Gilman AG, Goodman LS, Rall TW, Murad F (eds): The Pharmacological Basis of Therapeutics. 7th ed. New York, Macmillan, 1985, p 716

111. The ESVEM Investigators. Determinants of predicted efficacy of antiarrhythmic drugs in the electrophysiologic study versus electrocardiographic monitoring trial. Circulation 87:323, 1993
112. Zehenden M, Meinentz T, Faber T, Caspary A, et al. Antiarrhythmic effects of increasing the daily intake of magnesium and potassium in patients with frequent ventricular arrhythmias. J Am Coll Cardiol 29:1028, 1997
113. Arsenian MA. Magnesium and cardiovascular disease. Progr Cardiovasc Dis 35:271, 1993

18

Diagnosis and Management of Canine Arrhythmias

N. SYDNEY MOÏSE

OVERVIEW

The decision to treat an arrhythmia must be made in conjunction with the history, clinical signs, physical examination, and complete data base. Reasons for initiating treatment should be established and goals of therapy clearly understood by both the clinician and pet owner. Follow-up examinations and electrocardiographic (ECG) recordings are crucial to assure appropriate outcome.

ECG ACQUISITION AND ARRHYTHMIA IDENTIFICATION

ROUTINE ECG RHYTHM STRIP RECORDINGS

Routine ECG rhythm strips are frequently inaccurate and insufficient to disclose and assess potentially dangerous arrhythmias.[1, 2] Although standard ECG recordings may sometimes capture arrhythmias, reliance on these short recordings reduces the likelihood of arrhythmia detection, maintaining appropriate surveillance, or reaching accurate conclusions.

24-HOUR ECG (HOLTER) MONITORING

Twenty-four-hour ambulatory ECG (Holter) monitoring is an important technique to assist evaluation and monitoring, both before and after treatment. Three types of continuous ECG recorders are available:[2]

1. The continuous recorder (most commonly used in dogs and cats) contains at least two amplifiers and an analog tape recorder for capturing the ECG continuously;
2. The intermittent recorder is self-activated for purposes of capturing abnormal rhythms when a patient has symptoms. This records short segments for analysis or transmission by telephone;
3. The real-time analytic recorder analyzes the recording as it occurs and stores only information interpreted as abnormal.

CLINICAL INDICATIONS

A Holter recording is indicated whenever clinical signs may be associated with a cardiac arrhythmia that has eluded diagnosis on the routine ECG. In addition, animals with supraventricular tachycardia or ventricular tachycardia that requires treatment may benefit by comparing a baseline and post-treatment recording to evaluate efficacy.[3–7]

TECHNICAL PROCEDURE

The most valuable information results when Holter recordings are made in the home environment and combined with a pet owner diary describing the dog's activity and clinical signs. Many recorders have an event marker that can be activated by the owner. This identifies the time that a specific behavior such as syncope occurred. The techniques of lead placement and Holter monitor application have been described.[8] Technical problems include low-voltage QRS complexes, weak battery, motion artifact, poor electrode contact, tape drive malfunction, and incomplete degaussing of previously used tapes.

NORMAL FINDINGS AND DATA INTERPRETATION

Because commercial computerized Holter analyzers have algorithms designed for human adult interpretations, they cannot be automatically applied to canine or feline tapes without causing erroneous diagnoses. A tabulated report of the frequency of ectopic beats should not be accepted blindly, and examples of what were annotated as ectopic beats should be provided. Interactive reading by someone trained in the evaluation of animal electrocardiography provides a more accurate (and time-consuming) interpretation. In some instances, full disclosure of the 24-hour recording may be necessary.

ACCEPTABLE ARRHYTHMIA COUNTS. During prolonged ECG monitoring, a small number of clinically unimportant premature supraventricular and ventricular complexes may occur, even in healthy subjects.[2, 9] In humans, a Holter recording is considered within normal limits if premature complexes account for less than 100 beats/24 hr or less than 5 beats/hr, and no repetitive forms or complex arrhythmias occur.[10] Currently, there are no parallel guidelines for the dog and cat, although some observations can be mentioned. Although it is very uncommon to find ventricular arrhythmias in young dogs under 3 years of age, it is not unusual to record them in dogs over 8 years of age. Although this frequency increases with illness,[11] the clinical significance does not necessarily change. Holter recordings performed in normal beagles have revealed only rare ventricular extrasystoles.[9]

QRS VARIATION. A great variation in QRS-T morphology is present in canine 24-hour recordings. These may be caused by the change in cardiac location within the chest when the dog moves. Awareness of this fact prevents misdiagnosis of conduction disturbances.

NORMAL HEART RATE VARIATION. The normal healthy dog may have sinus rates that approach 300 beats/min and last for a short time during excitement or acute pain. Such heart rates can develop relatively rapidly without an obvious "warm-up" period, especially with recordings printed at a maximum of 25 mm/sec. This may lead to a mistaken diagnosis of a pathologic and serious supraventricular tachyarrhythmia. Conversely, sinus rates of 25 to 35 beats/min during deep, slow-wave, or rapid eye movement sleep are not unusual in the dog.[12, 13] Also, during these stages of sleep prolonged sinus pauses of 2 to 4 seconds occur. Such pauses could be misdiagnosed as evidence of sick sinus syndrome if a diary of the dog's activity is not kept. Some normal sleeping dogs will develop junctional or even ventricular escape rhythms during sleep. In young, healthy dogs, occasional second-degree atrioventricular (AV) block can occur, even in the midst of a normal sinus rhythm.

TACHYARRHYTHMIAS: VENTRICULAR VS. SUPRAVENTRICULAR

The origin of tachyarrhythmias is classified as either *supraventricular* or *ventricular*. In Table 18–1, the most reliable distinguishing criteria have been listed, although there are exceptions. In humans, the QRS complex morphology recorded in precordial leads has led to specific algorithms for differentiation;[14–16] how-

TABLE 18–1
Differentiation of Supraventricular and Ventricular Arrhythmias

Supraventricular		Ventricular
Narrow	Is the QRS complex narrow or wide?	Wide
Yes	Does the premature complex look 80–90% like the normally conducted sinus complex?	No
Yes	Are P waves associated with the premature QRS complexes?	No
No	Are fusion beats present?	Yes

ever, these remain to be studied in spontaneous canine arrhythmias.

MORPHOLOGY OF THE QRS COMPLEX

Premature QRS complexes of supraventricular origin usually appear as normally conducted sinus complexes (Fig. 18–1), which are usually narrow when compared with complexes of ventricular origin. Supraventricular tachyarrhythmias are most commonly confused with ventricular tachyarrhythmias when the QRS complex is wide (Fig. 18–2). A wide tachycardia of supraventricular origin occurs with (1) marked ECG evidence of left or right ventricular enlargement, (2) pre-existent left or right bundle branch block, (3) AV conduction over an accessory pathway, and (4) functional left or right bundle branch block (aberrancy). "Aberrancy" is a term used to indicate that conduction was delayed because the premature stimulus triggered a QRS complex when some myocardial cells were partially refractory. Therefore, the QRS complex has a different configuration than the normal sinus complex. Because the recovery time of the right bundle branch is longer than that of the left, the aberrant complex usually has the configuration of a right bundle branch block. Although aberration is usually considered with premature complexes (acceleration-dependent or long-short aberration), it can occur with slow heart rates (deceleration-dependent aberration) (Fig. 18–3). Commonly, the T-wave configuration is different in size or polarity with premature supraventricular complexes even though the QRS complex is almost identical to the sinus complex (see Fig. 18–1). Uncommonly, premature ventricular complexes (PVCs) can appear narrow and very similar to the normally conducted sinoatrium-initiated complex. This can be true if the origin of the PVC is near the His bundle,[17] or it may be noted in only a single lead.[8] Therefore, simultaneously recorded leads should be examined.

ASSOCIATION OF P WAVES AND QRS COMPLEXES

When P waves are dissociated from QRS-T complexes, the arrhythmic QRS waveform is most likely of ventricular origin. Such an identification may be difficult with ventricular tachycardia (VT), particularly when sinus-initiated P waves are hidden within the

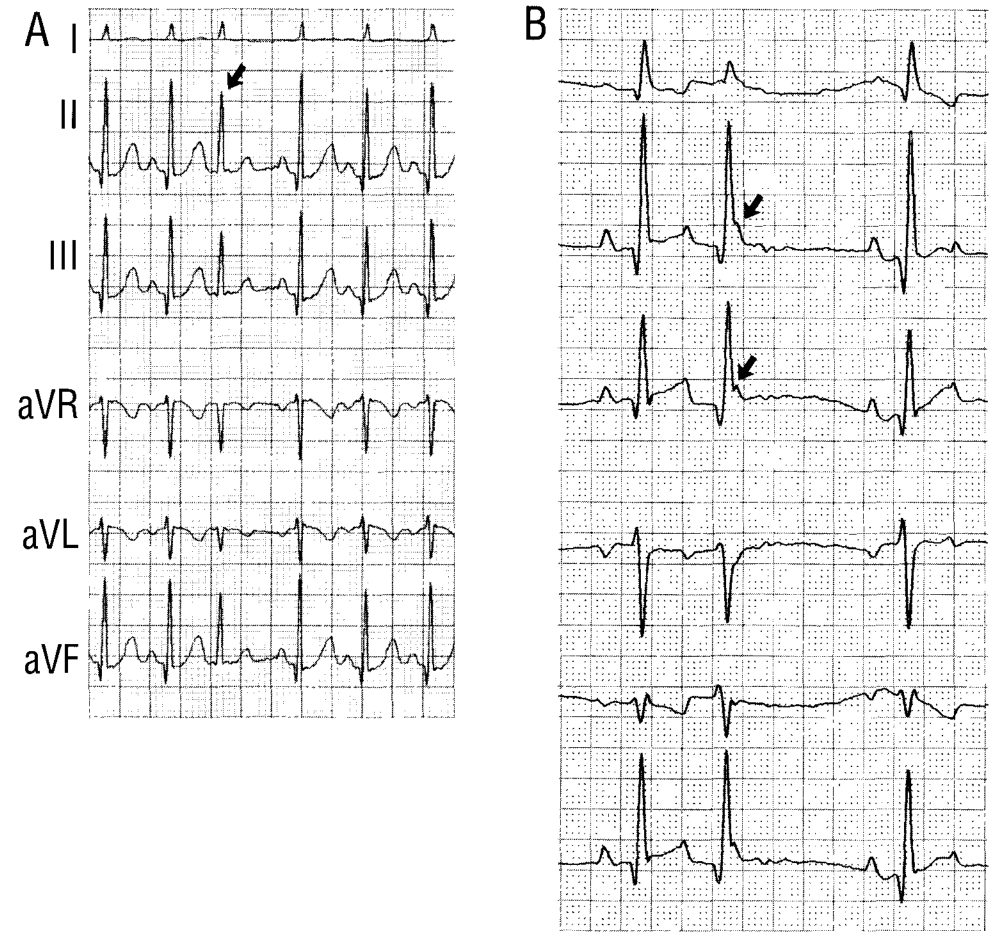


FIGURE 18–1

Composite illustrating canine premature supraventricular complexes. The QRS morphology of these complexes is narrow and appears similar to complexes originating from the sinoatrial node. Interpretation is more accurate when simultaneously recorded leads are examined. Paper speed 50 mm/sec, 1 mV = 1 cm. (A) Sinus tachycardia with a premature supraventricular complex *(arrow)* is present. Its morphology is narrow (supporting supraventricular origin) but slightly different from the QRS complexes of sinus origin. The amplitude is smaller, and the initial depolarization forces are altered (note the lack of a Q wave in II, III, and aVF and the lack of an r-wave in aVR and aVL) due to aberrancy. Even when a premature QRS complex appears identical to the sinus complex, the T-wave morphology can be different as noted here. (B) The configuration of the premature complex (second from left) is slightly altered, not because of aberrancy but because of a superimposed P wave *(arrows)*.

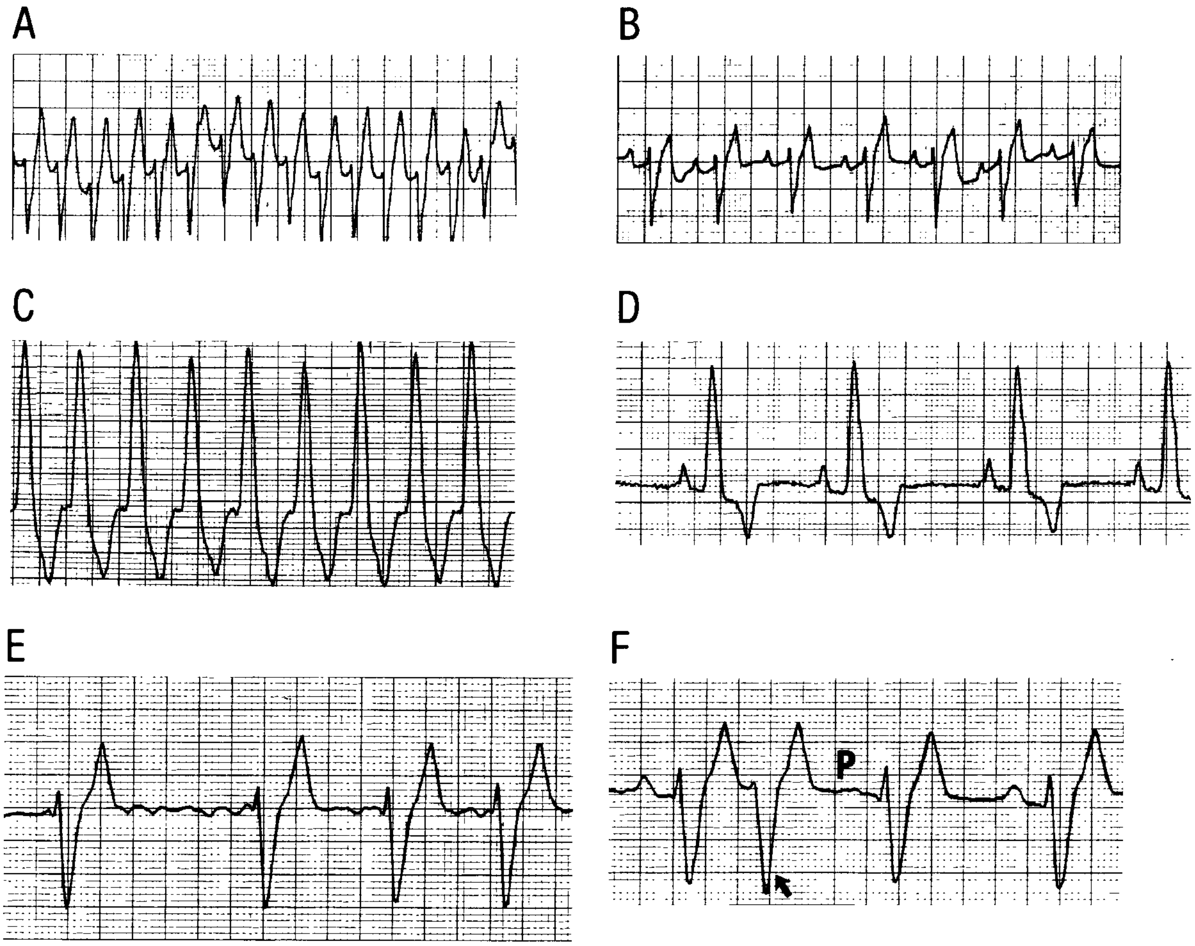


FIGURE 18–2

Composite of canine supraventricular tachycardias with wide QRS complexes that can be mistaken for ventricular tachycardias. Paper speed 50 mm/sec, 1 mV = 1 cm, lead II. (A and B) This 6-month-old cocker spaniel was undergoing a balloon valvuloplasty for severe pulmonic stenosis. Sinus tachycardia is present (A). When the heart rate slows, a sinus rhythm (note P waves for each QRS-T complex) with evidence of right ventricular hypertrophy is apparent. (C and D) This rapid, wide QRS complex supraventricular arrhythmia resembles ventricular tachycardia (C). When the tachycardia breaks (D), a sinus rhythm with left bundle branch block is evident. (E and F) ECGs recorded from a Saint Bernard. The QRS complexes are negative, wide, and abnormal in polarity for lead II (characteristic of a right bundle branch block). (E) An irregular rhythm without P waves (fine fibrillation waves are present) constitutes atrial fibrillation. In (F), the atrial fibrillation converted to a sinus rhythm and distinct P waves *(P)* are evident. An atrial premature complex is illustrated *(arrow)*. The following sinus complex has a P wave that is very different in configuration from the other P waves. This wider, lower-amplitude P wave results from aberrant atrial conduction caused by the previous premature complex, and it is known as *Chung's phenomenon*.

QRS-T complex, or if retrograde atrial depolarizations occur. In the latter, complexes that originate in the ventricle conduct retrograde through the atrioventricular node to depolarize the atrium; the resulting negative P wave is hidden in the QRS-T complex.[18]

With supraventricular arrhythmias, P waves may not be visible if they are hidden in the preceding T wave (Fig. 18–4). In humans, premature atrial P waves look different from those of sinus origin. However, this is frequently unreliable in the dog because the sinus node is large (40 mm),[19] and impulses emerge from different regions, depending on autonomic tone. This causes variation in P-wave configuration (*wandering pacemaker*) with sinus complexes (Fig. 18–5). Another cause of P waves that are not associated with QRS-T complexes is *junctional tachycardia*. Although a junctional tachycardia can depolarize the atria, it is possible for this supraventricular arrhythmia to have the atria controlled by the sinus node or other atrial tissue (Fig. 18–6).

REGULAR OR IRREGULAR RHYTHM

Determining whether the rhythm is regular or irregular, and the length of the pause following a premature complex, are unreliable features to consider in

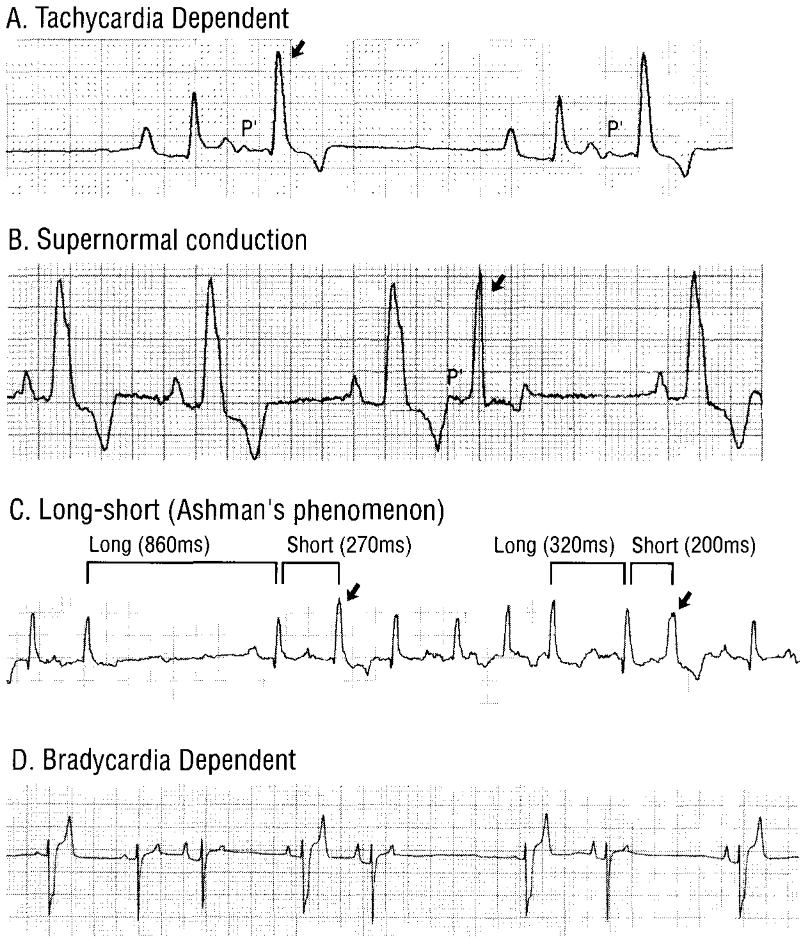


FIGURE 18–3

Composite of premature supraventricular complexes with altered conduction caused by the timing of the stimulus. Paper speed 50 mm/sec except (D), which is 25 mm/sec, 1 mV = 1 cm.

(A) ECG recorded from a dog with atrial bigeminy exemplifies acceleration-dependent aberration. The arrow points to the aberrant R wave. Notice also the associated premature P′ wave. Aberrant conduction that widens the premature supraventricular complex is usually acceleration dependent. This occurs when the ventricle is stimulated by premature stimulus during the relative refractory period. It results in delayed ventricular conduction that prolongs the QRS morphology of the atrial premature complex.

(B) ECG recorded from a 14-year-old Ibizan hound with left bundle branch block. Although excessively premature supraventricular complexes usually result in slower ventricular conduction, supernormal conduction can occasionally occur. In supernormal conduction, the P-R interval remains unchanged or shortened as seen here. This finding rules out equal prolongation of the left and right bundle branches. Although the name implies conduction that is faster than normal, the actual meaning is conduction that is better than expected. Here, a supraventricular premature complex *(arrow)* results in a QRS complex, which is narrower than that associated with the sinus rhythm. The T-wave configuration is also altered. The other reason for such a narrow complex is equalization of conduction between the left and right bundle branches. In such a case the right bundle is delayed with the premature stimulation. Therefore, with the pre-existing delay in the left bundle, the conduction time is more synchronized and the cancellation of forces results in a narrow complex.

(C) ECG from a 9-year-old mixed-breed dog. Aberrant conduction depends not only on the degree of prematurity of a stimulus, but also on the R-R interval that immediately precedes the premature beat. This is because the action potential duration of a beat is determined by the preceding R-R interval. The longer the R-R interval, the longer the action potential and the greater the possibility for aberration. This type of aberrancy has been named Ashman's phenomenon and is associated with a long-short sequence. That is, a normally conducted complex occurs after a long R-R interval, but aberration develops when the next stimulus occurs after a short R-R interval. Although this type of aberration most commonly affects the right bundle, left bundle branch block (LBBB) or prolongation also occurs, as shown in this tracing. The first beat *(arrow)* of the supraventricular tachycardia is widened with an LBBB pattern. After this complex, accommodation develops to the fast rate, and a narrow tachycardia persists until another long-short sequence results in an aberrant complex *(second arrow)*. This dog had atrial tachycardia, although this type of aberrancy is more often associated with atrial fibrillation because of the more frequent variation in the R-R intervals. Numbers between R waves indicate R-R interval duration in msec.

(D) ECG from an 8-year-old Afghan hound exhibiting deceleration-dependent aberration. Notice that incomplete right bundle branch block alternates with complete right bundle branch block at slow heart rates (R-R intervals >440 msec). Before the development of the deceleration-dependent complete RBBB, the dog had incomplete RBBB for 5 years without clinical signs. The variation in R-R interval was due to sinus arrhythmia.

differentiating supraventricular and ventricular rhythms. A regular or irregular rhythm can occur with both. Identification of compensatory or noncompensatory pauses is frequently not useful because of sinus arrhythmia, interpolated premature complexes, and retrograde atrial depolarization with resetting of the sinus node by ventricular complexes.[20, 21]

USING VAGAL MANEUVERS TO ASSIST DIFFERENTIATION

Interventions that increase vagal tone to the heart may profoundly alter supraventricular arrhythmias. Therefore vagal maneuvers (Fig. 18–7) or intravenous (IV) administration of cholinergic drugs may help distinguish some ventricular from supraventricular tachyarrhythmias and assist in classifying supraventricular tachycardia as AV nodal dependent or independent (see later). Vagal tone is physiologically increased by the Valsalva maneuver (humans),[22] coughing, sneezing, gagging, or vomiting.[23] Some physical maneuvers (sitting down, head-dependent position, cold immersion, and deep breath) increase systemic blood pressure and reflexly activate vagal tone.

CAROTID SINUS MASSAGE

The most clinically useful maneuver to increase vagal traffic to the heart is carotid sinus massage (Fig.

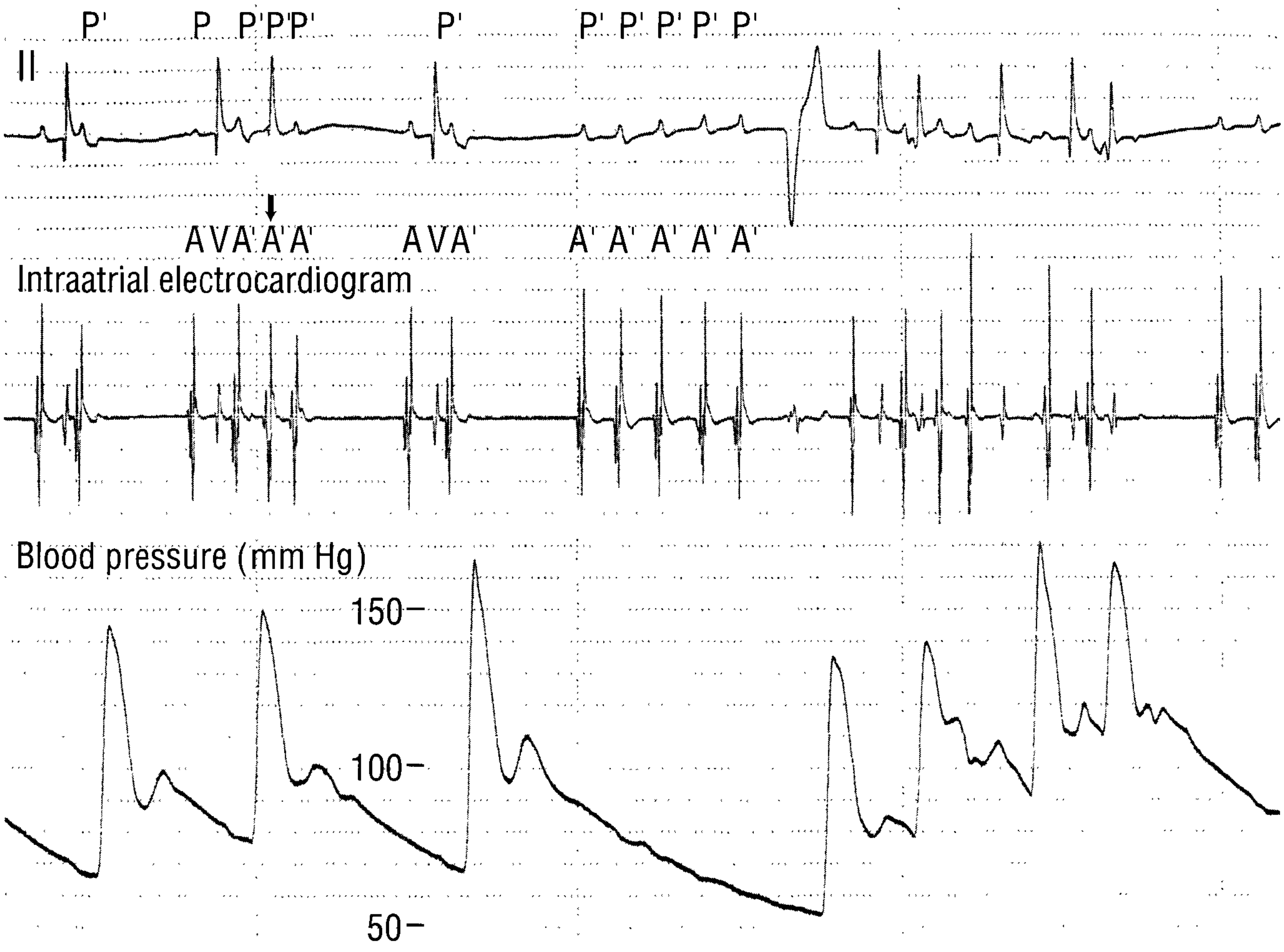


FIGURE 18–4

Electrophysiologic recordings from a German shepherd dog who developed supraventricular arrhythmias during anesthesia using a fentanyl infusion. A lead II ECG recording reveals ectopic P′ waves. Because of the high vagal tone induced by the fentanyl, many ectopic P′ waves are not conducted, and a ventricular escape complex is evident following five sequential P′ waves. A simultaneously recorded intra-atrial electrogram shows the A and A′ waves. Atrial depolarizations (A′) are evident on the intra-atrial electrogram, but some of the corresponding P′ waves are not distinguishable on the surface lead II ECG because the P′ wave is hidden within a QRS complex *(arrow)*. Notice the effect of the arrhythmia on arterial blood pressure. Paper speed 25 mm/sec.

18–7). Elevated vagal tone slows the sinus rate because of (1) hyperpolarization (activation of channel I_{KACH}), and (2) inhibition of channels that promote depolarization during hyperpolarization (I_f).[24–26] AV nodal conduction is slowed (particularly the N or central/compact region) because of hyperpolarization and diminished action potential amplitude.

The dog should be positioned in lateral recumbency, with care taken to calm the pet. The points of maximal carotid arterial pulse are palpated with the fingertips placed behind the angle of the jaw on the right and left upper neck. Here, firm, medially directed pressure is initiated over the carotid arteries for 5 to 10 seconds. This is applied by moving the fingertips longitudinally, back and forth in a craniocaudal direction. The imposed pressure stimulates baroreceptors in the carotid sinuses. Emanating from the carotid sinus, a branch of the 9th cranial nerve (the nerve of Hering) travels up to the vasomotor center of the medulla.[27] If effective nerve stimulation has occurred, the accompanying increase in efferent parasympathetic traffic to the heart and decrease in sympathetic tone will slow the sinus heart rate and AV nodal conduction, cause peripheral vasodilation, and reduce systemic blood pressure.[28] Once the maneuver is stopped, the sympathetic nervous system will counteract the imposed autonomic imbalance (Fig. 18–7).

Experimentally, direct stimulation of the canine vagus nerve causes dramatic reduction in heart rate and AV nodal conduction. However, if sympathetic tone is elevated, carotid sinus massage may not terminate the supraventricular tachycardia (SVT). Heightened sympathetic tone that overrides increased parasympathetic activity is one reason why vagal maneuvers are fre-

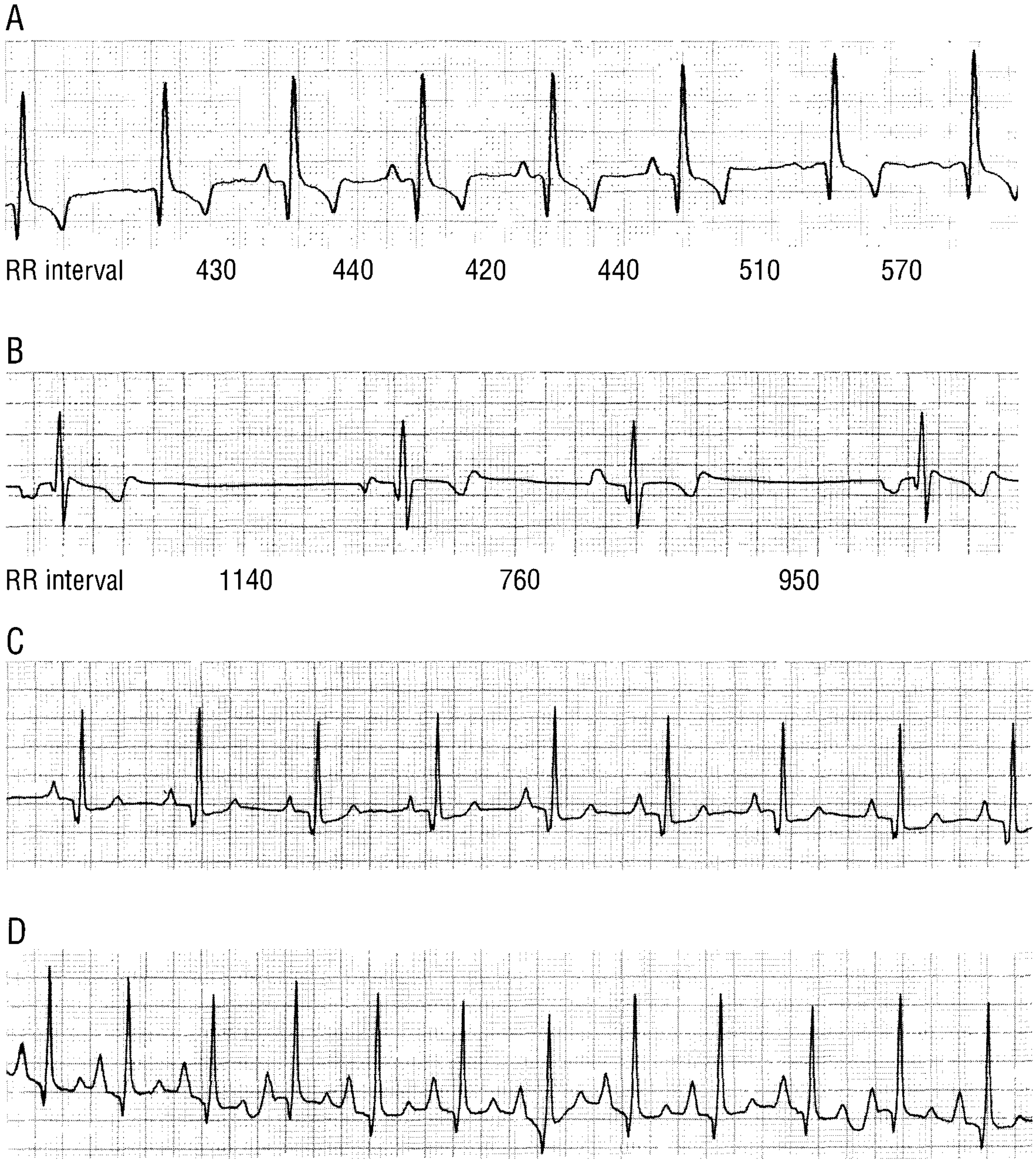


FIGURE 18–5

ECGs recorded from normal dogs to illustrate the effect of autonomic tone and P-wave configuration (R-R intervals are in msec). Paper speed 50 mm/sec, 1 mV = 1 cm, lead II. (A) The changing size and shape of the P wave, known as *wandering pacemaker*, is caused by a shift in sinus impulse origin within the large canine sinoatrial node. During respiratory sinus arrhythmia, the balance of autonomic tone shifts during expiration to the parasympathetic, and during inspiration, to the sympathetic. This results in an alternating slower and faster heart rate, respectively, and shifts the site of sinus origin. During the slower sinus heart rate, the P wave is shorter, whereas during the faster heart rates the P wave is taller. Typically, the P wave is taller during sinus tachycardia. During prolonged R-R intervals (exaggerated sinus arrhythmias), the P wave after the long pause is occasionally tall. This may be due to elevated sympathetic tone in response to the prolonged drop in blood pressure, shifting the focus of SA nodal discharge to a more ventral location in the sinus node.
(B) ECG from a dog with a pronounced sinus arrhythmia. Notice the wide spectrum of P-wave configurations with a wandering pacemaker. The negative P waves (first and last beats) probably originate near the coronary sinus. (C) was recorded from a dog during sinus rhythm, whereas (D) was recorded from the same animal immediately after exercise. The P-wave amplitude increased in response to sympathetic stimulus and heart rate.

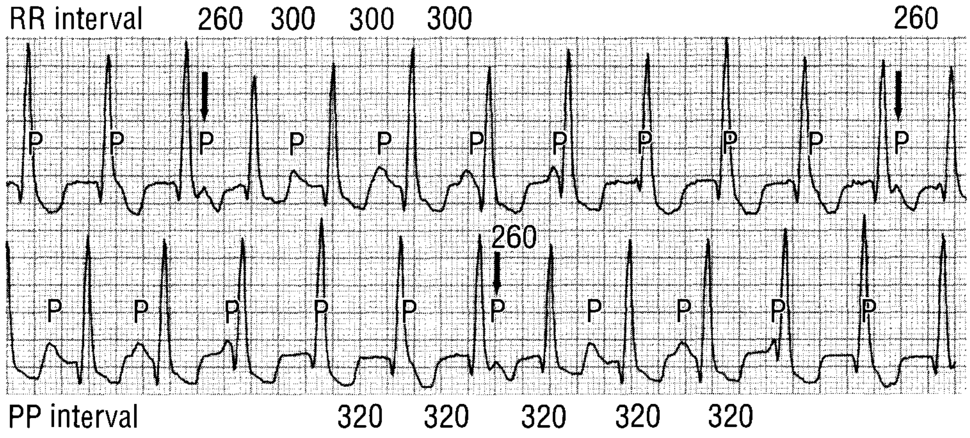


FIGURE 18–6

ECG from an English bulldog, with supraventricular tachycardia originating from the atrioventricular nodal region. Sinus P waves are evident that are not associated with the tachycardia. Occasionally, there was SA capture (notice the P waves *[arrows]* associated with QRS-T complexes), resulting in a shorter R-R interval (260 msec). This example illustrates junctional tachycardia with occasional capture. Numbers indicate P-P and R-R interval duration (msec). Paper speed 50 mm/sec, 1 mV = 1 cm, lead II.

quently ineffective, and this heightened tone may require adjunctive, cautious administration of drugs that affect the sinoatrial or AV nodes (e.g., β-adrenergic blockers or calcium channel blockers). Repeating vagal maneuvers may then induce AV block or break the tachyarrhythmia (Fig. 18–8).

SUPRAVENTRICULAR TACHYARRHYTHMIAS

Supraventricular arrhythmias originate from the atria or the AV junction. Antiarrhythmic drugs work through their effects on ion channels, which, in turn, affects the underlying mechanism of the arrhythmia. Thus, inference of mechanism could serve as the basis of more rational drug selection. Although differentiating causal mechanism is difficult,[29] some guidelines may be offered.

AV NODE INDEPENDENT VS. AV NODE DEPENDENT SUPRAVENTRICULAR TACHYCARDIAS

Some SVTs are characterized by their requirement for the AV node; SVTs that do not need the AV node to perpetuate the abnormal rhythm are *AV node independent.* These include ectopic atrial tachycardias (automatic, triggered, intra-atrial re-entrant), sinoatrial node tachycardias (automatic, re-entrant), atrial flutter, and atrial fibrillation. Conversely, those rhythms that require the AV node for existence are *AV node dependent.* These include AV nodal re-entrant tachycardia, automatic junctional tachycardia, and bypass tract tachycardia. Their differentiation can be assisted by response of increases in parasympathetic tone (vagal maneuvers) and drugs that affect AV nodal conduction. For example, if parasympathetic tone is effectively increased, the following may occur: (1) automatic sinus tachycardia is gradually slowed; (2) ectopic atrial tachycardias usually persist, but the ventricular rate is slowed and P waves (AV block) may be identified; (3) the F waves of atrial flutter and f-waves of atrial fibrillation are exposed, and ventricular response is decreased; and (4) the arrhythmia of AV nodal reentry can be abolished.

AV NODE INDEPENDENT SUPRAVENTRICULAR TACHYCARDIAS

SINUS NODE TACHYCARDIA

DEFINITION, ECG FEATURES, MECHANISMS. Sinus node tachycardia is characterized by positive P waves in leads II, III, and aVF. The tachycardia increases (onset) and decreases (offset) gradually rather than abruptly;[30] the heart rate is not instantly at its maximum, but acceleration develops with progressively shorter P-P intervals and associated R-R intervals. Similarly, the offset of the arrhythmia does not occur suddenly, but progressive lengthening of the P-P and R-R intervals occurs before the arrhythmia stops. These changes in rate can occur over only a few beats. Gradual speeding (warm-up) and slowing (cool-down) of heart rate is characteristic

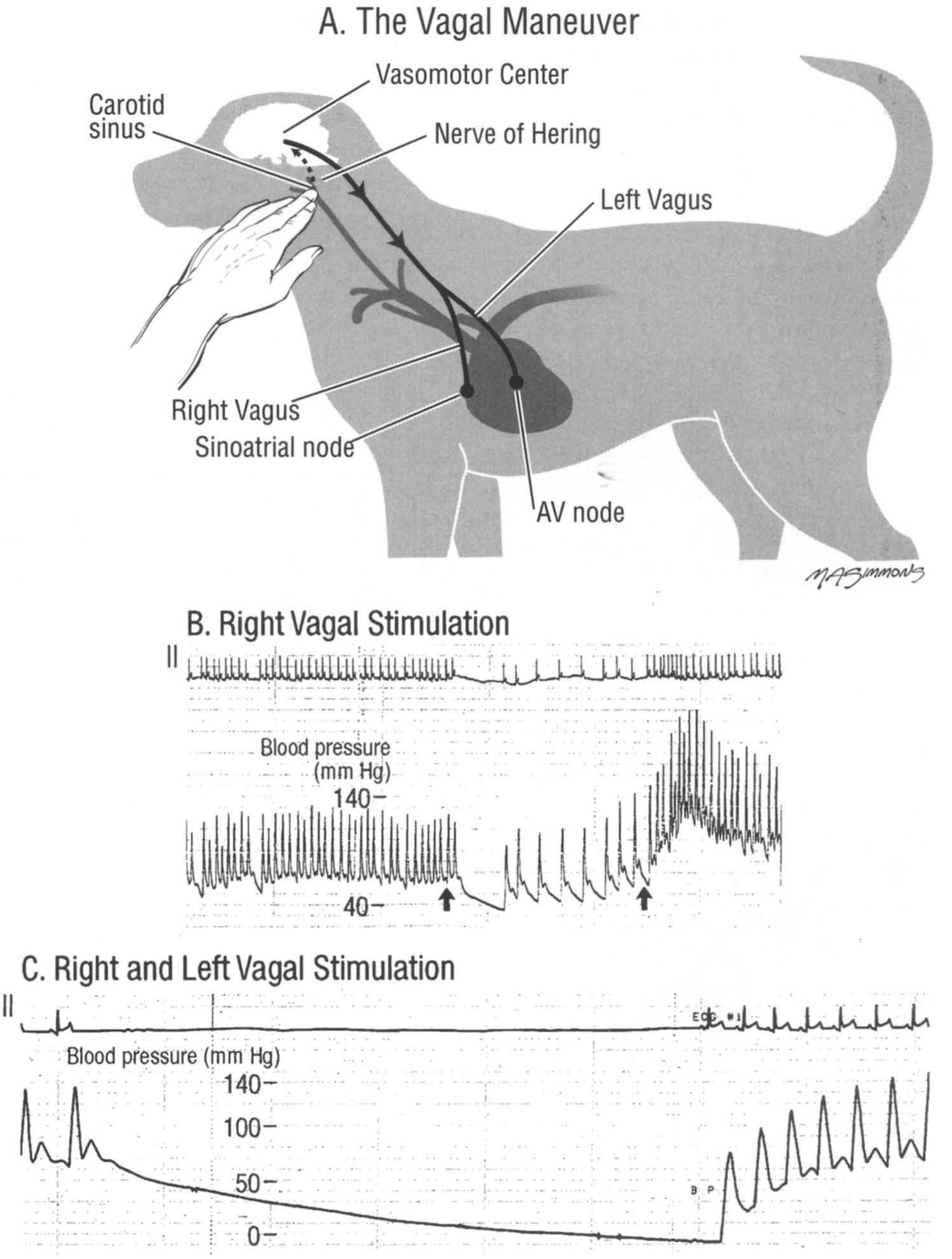


FIGURE 18–7

Parasympathetic tone can be increased by direct carotid sinus massage. (A) Digital pressure applied to the carotid sinus directly stimulates associated baroreceptors. The nerve of Hering, a branch of the 9th cranial nerve, transmits afferent impulses to the vasomotor center of the medulla. This stimulates the vagus (10th cranial) nerve, resulting in efferent cardiac traffic that reduces sinoatrial node discharge (decreasing heart rate) and slows atrioventricular node conduction. Atrial and, to the least extent, ventricular myocardium also are affected by the increased vagal traffic. (B) Simultaneous Lead II ECG and arterial blood pressure recording in a dog. The first arrow indicates the time when its cervical right vagus nerve was directly stimulated experimentally. Notice the reduction in heart rate and blood pressure. When stimulation was stopped shortly after *(second arrow)*, a rebound increase in heart rate and blood pressure occurred. This degree of response can sometimes occur clinically with successful carotid sinus massage. Paper speed 10 mm/sec. (C) Simultaneous experimental direct stimulation of both the right and left vagal nerves in the same dog elicited a profound reduction in heart rate and blood pressure. This represents a far greater response than occurs when carotid sinus massage is clinically applied—unless underlying sinus node disease is present. Paper speed 10 mm/sec.

of arrhythmias caused by enhanced automaticity. While heart rates approaching 300 beats/min can develop in a frightened dog, such rates are not sustained. Dogs with cardiac pathology or systemic diseases can develop more sustained automatic sinus tachycardia. An *inappropriate sinus tachycardia* has been described in humans,[29] not associated with physiologic or pathologic conditions.

EFFECT OF VAGAL MANEUVERS, DRUG INTERVENTIONS. Vagal maneuvers may cause gradual slowing of the heart rate. In dogs that have sinus node tachycardia secondary to severe pulmonary edema, cardiac tamponade, or shock, heart rate is usually reduced after pharmacologic control or correction of the underlying problem.

SINUS NODAL RE-ENTRANT TACHYCARDIA

DEFINITION, ECG FEATURES, MECHANISMS. This rhythm is characterized by positive P waves in leads II, III, and aVF. Because this is a re-entrant tachyarrhythmia, the onset and offset are usually abrupt without a warm-up period.[31, 32] While re-entrant SVT that involves the sinus region is uncommon and questionable in humans,[30, 33] its frequency in the dog is unknown. The large size of the canine sinus node[19] may provide greater likelihood

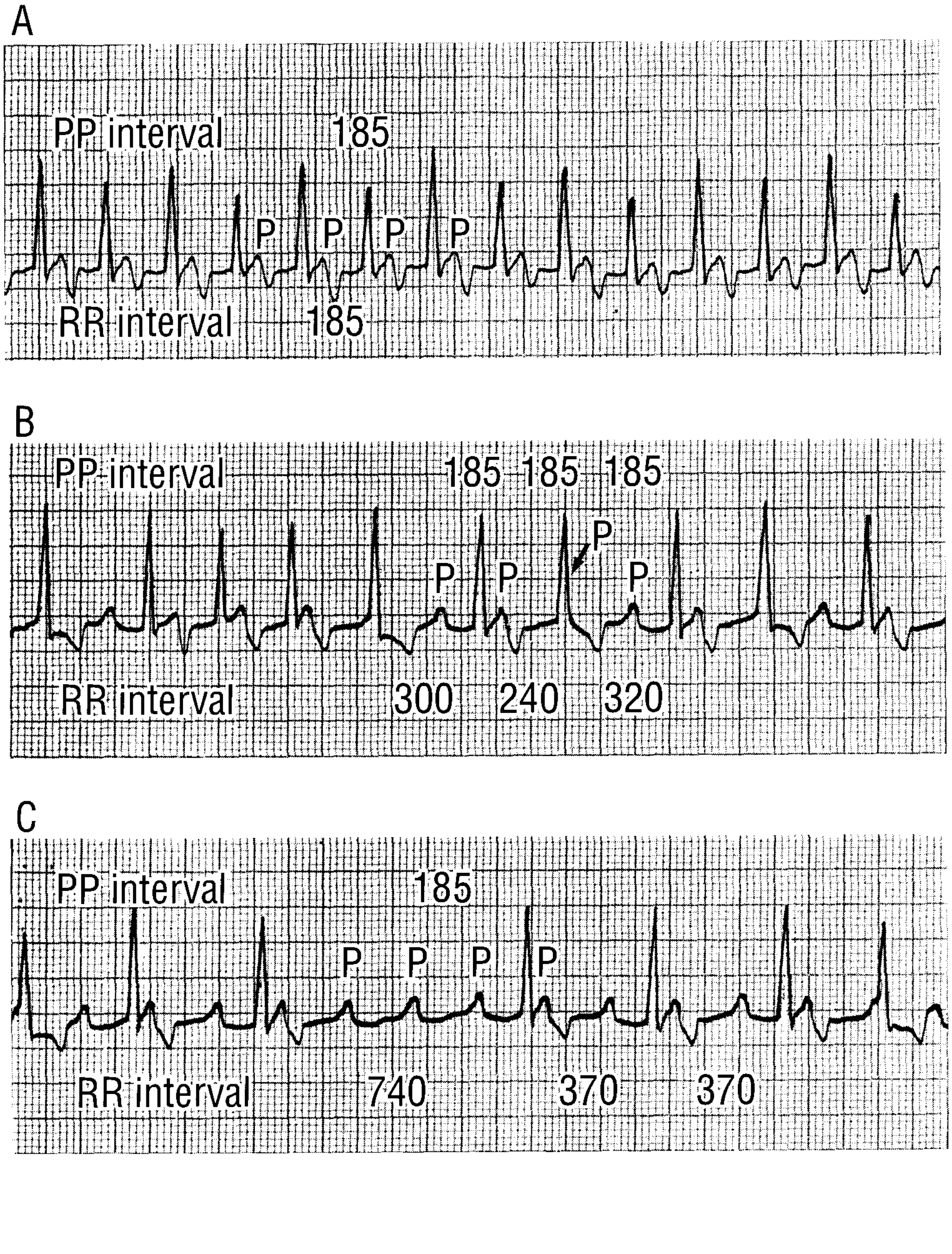


FIGURE 18-8

AV node independent supraventricular tachycardia in a 7-year-old Saint Bernard. In each tracing, numbers indicate the P-P interval *(top)* and R-R interval *(bottom)*. Paper speed 50 mm/sec, 1 mV = 1 cm, lead II. (A) A narrow QRS tachycardia (>300 beats/min) is present; QRS complexes alternate in amplitude due to alternating aberrancy. This results from the rapid supraventricular tachycardia rate. Obscured P waves *(P)* were suspected in the ST segment. (B) After IV propranolol administration, AV nodal conduction slowed, and the resulting ventricular response rate was reduced because of progressive AV block. Blocked P waves *(P) (arrow)* occur. (C) Carotid sinus massage was then repeated after β-adrenergic blockade, which further decreased AV nodal conduction. A more advanced AV block resulted (notice nonconducted P waves). Although this decreased the ventricular rate, the underlying supraventricular tachycardia persisted unchanged (P-P interval, 185 msec).

for its occurrence, particularly since it supports decremental conduction (increased conduction time with increasing prematurity of the stimulus)[31, 32] and unidirectional block, which favor re-entry.

EFFECT OF VAGAL MANEUVERS, DRUG INTERVENTIONS. The re-entrant loop involves the sinus node. Therefore, increases in vagal tone or drugs that affect these slow calcium channel cells (e.g., calcium channel blockers, β-blockers, digitalis glycosides, or adenosine) would abolish the arrhythmia.[31, 32]

ECTOPIC ATRIAL TACHYCARDIA

DEFINITION, ECG FEATURES, MECHANISMS. These arrhythmias originate from atrial myocardium. When the cause is abnormal automaticity[34] or triggered activity,[35–41] the ECG is characterized by (1) P′-wave configuration and polarity that vary with the location of ectopic origin, (2) gradual onset (however, an irregular P′-P′ interval is common initially), and (3) gradual offset of tachycardia with prolongation of the P′-P′ interval (Fig. 18–9). A common SVT seen in the dog is one that also is characterized by a positive P wave in leads II, III, and aVF, slight warm-up and cool-down of the P-P interval, and frequently, just before termination of the tachycardia, an increase in the P-R interval. This rhythm most likely is an atrial tachycardia, although inappropriate sinus tachycardia cannot be excluded.[29]

EFFECT OF VAGAL MANEUVERS, DRUG INTERVENTIONS. Vagal maneuvers or drugs that slow AV nodal conduction usually do not abolish ectopic atrial arrhythmias, but they can decrease the ventricular response rate (see Fig. 18–8). However, some automatic atrial tachycardias are influenced by autonomic tone and potentially can be terminated and prevented with β-adrenergic blocking drugs. The SVTs caused by abnormal automaticity are frequently difficult to control, even with class IA and class III drugs. Vagal maneuvers might abolish triggered atrial tachycardias by increasing parasympathetic tone. This activates the potassium channel I_{KACh}, which shortens the action potential in atrial myocytes, thereby decreasing the probability of triggered activity or re-entry. When triggered activity is the mechanism for SVT, calcium channel blockers may abolish the arrhythmia.[42–44] The positive P′-wave SVT seen in dogs frequently responds to aggressive increases in vagal tone, β-adrenergic blockade, and calcium channel

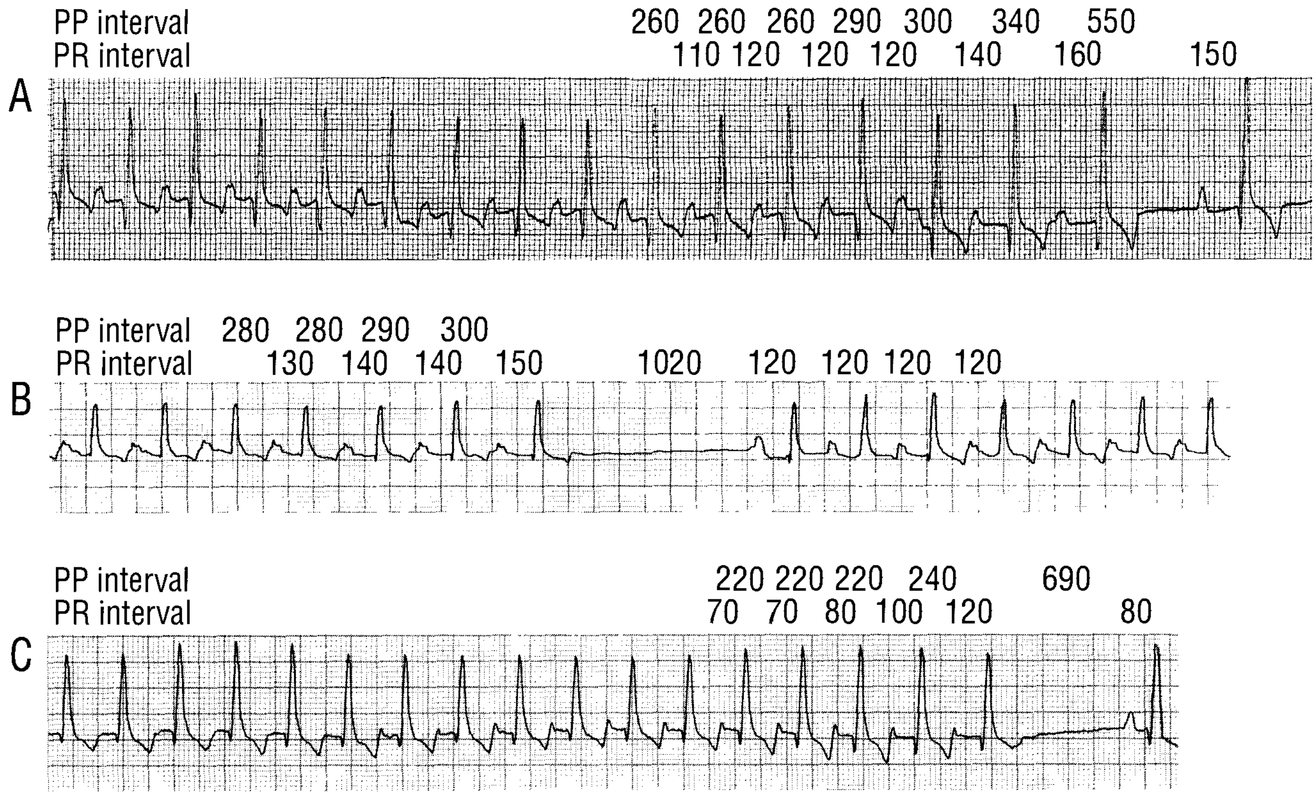


FIGURE 18–9

Lead II ECGs showing ectopic atrial tachycardias characterized by (1) positive P′ waves, (2) gradual offset of tachycardia with prolongation of the P′-P′ interval, and (3) prolonged P′-R′ interval in the last few complexes of the tachycardia preceding termination. Paper speed 50 mm/sec, 1 mV = 1 cm.

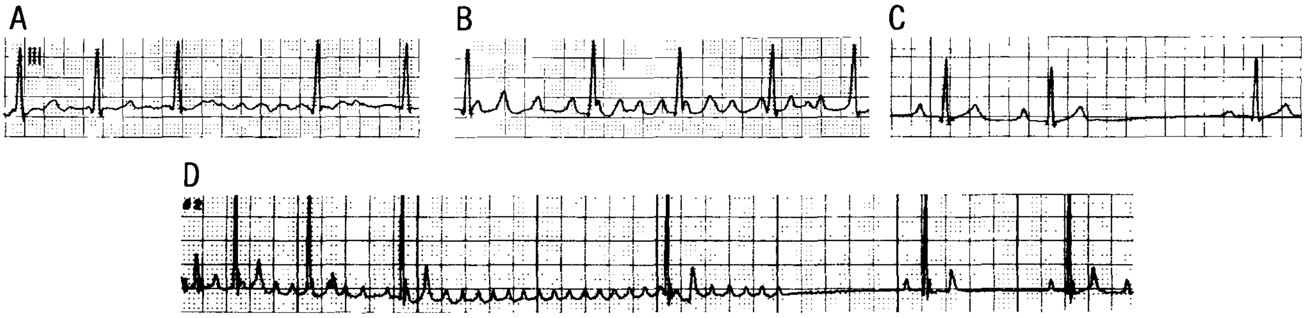


FIGURE 18–10

These ECGs recorded from a normal, healthy, 2-year-old Rhodesian ridgeback illustrate intermittent atrial fibrillation and flutter. (A), (B), and (C) were recorded within 5 minutes of each other. Intermittent coarse atrial fibrillation (A) and flutter (B) were present. The dog would spontaneously convert to a sinus rhythm (C). Paper speed 50 mm/sec, 1 mV = 1 cm, lead II. (D) On a 24-hour Holter recording, spontaneous conversion of atrial flutter to sinus rhythm is captured. Treatment with flecainide decreased the frequency of the atrial fibrillation and flutter by 90%. Paper speed 25 mm/sec, 1 mV = 1 cm.

blockade. Drugs that increase the refractory period and slow conduction velocity in the atrial myocardium, such as procainamide, quinidine, propafenone, or amiodarone, should have an antiarrhythmic effect. Accordingly, these are usually chosen to treat ectopic atrial tachycardias when conversion, rather than control of ventricular response rate, is the goal.[37, 38, 45, 46]

ATRIAL FLUTTER

DEFINITION, ECG FEATURES. Sawtooth-shaped, rapid undulations (F waves) replace distinct P waves. Very rapid atrial flutter can be a transition to atrial fibrillation, whereas slow atrial flutter may convert to a sinus rhythm. In dogs, atrial flutter is an unstable rhythm and can occur intermittently (Fig. 18–10). Flutter waves have a constant morphology, polarity, and cycle length that usually ranges from 300 to 600 beats/min.

MECHANISMS. A macrore-entrant circuit usually travels around the caudal vena cava, crista terminalis, and cranial vena cava.[47–50] The ventricular response with atrial flutter is usually rapid and irregular, unless 2:1 conduction occurs. Flutter with 2:1 conduction may be

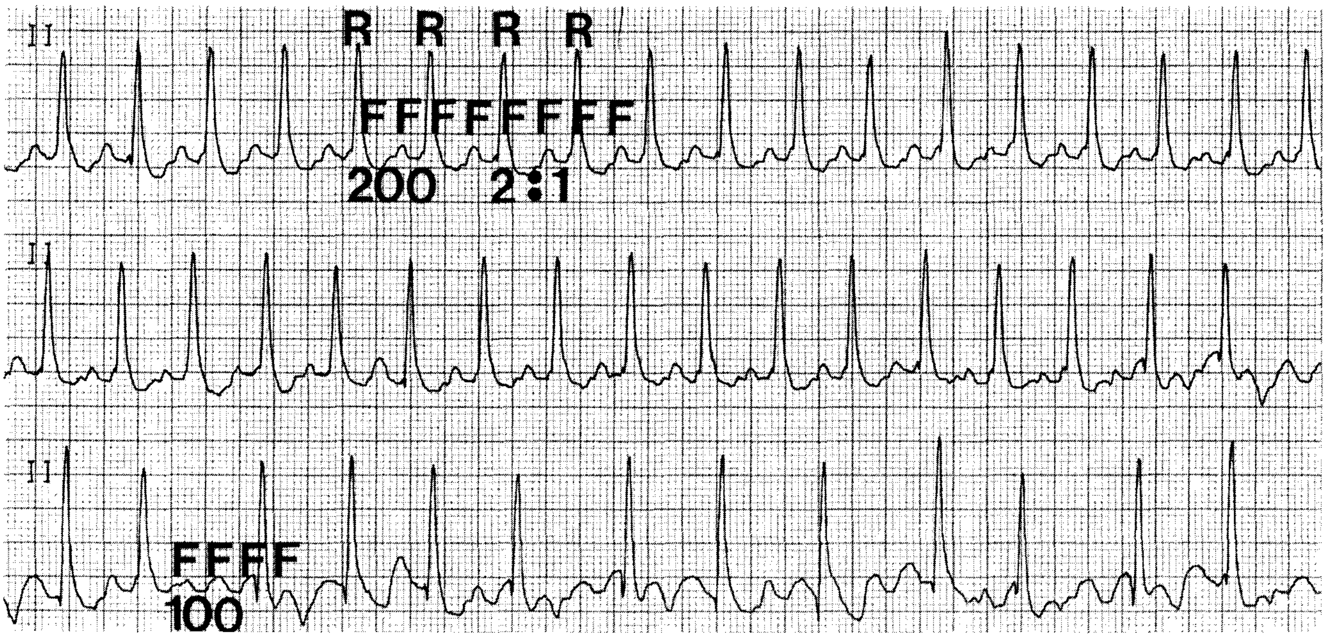


FIGURE 18–11

Differentiating atrial flutter from other supraventricular rhythms can be difficult when 2:1 conduction exists, as in the top and middle traces (R-R interval, 200 msec; F-F interval, 100 msec). A vagal maneuver slowed AV nodal conduction to 3:1 (beginning of the third tracing), which exposed the F waves and facilitated diagnosis. Paper speed 50 mm/sec, 1 mV = 1 cm, lead II.

difficult to distinguish from other types of SVT because F waves cannot be identified. When the T wave is equally spaced between two R waves, atrial flutter should be suspected (*Bix rule*) (Fig. 18–11).[51]

EFFECT OF VAGAL MANEUVERS, DRUG INTERVENTIONS. Vagal maneuvers and drugs that slow AV nodal conduction do not abolish atrial flutter, but they can reduce the ventricular response rate. If conversion or prevention is the goal, drugs with class Ia antiarrhythmic properties have been used; however, drugs in class Ic (propafenone, flecainide) or class III (amiodarone) may be more effective.[52, 53]

ATRIAL FIBRILLATION

DEFINITION, ECG FEATURES. Atrial fibrillation (AF) is a common supraventricular tachyarrhythmia SVT.[54–57] The fibrillation waves seen in dogs with cardiac disease are characterized by fine, irregular, baseline undulations. Distinct P waves are not present. Although as many as 700[58–60] atrial impulses/min arrive at the AV node, the ventricular response is almost always irregular because only a few impulses traverse the entire AV node to reach the ventricles (Figs. 18–12, 18–13).

MECHANISMS. Atrial fibrillation is a microre-entrant arrhythmia that has a number of predisposing factors. A brief description appears here:

CRITICAL MASS. Atrial fibrillation requires a myocardial area of adequate size or critical mass. Large hearts fibrillate longer than small hearts.[61] Atrial fibrillation in dogs with cardiac disease is usually sustained because the atria are enlarged, although occasionally paroxysmal episodes occur. Some giant-breed dogs develop AF without demonstrable cardiac enlargement or pathology.

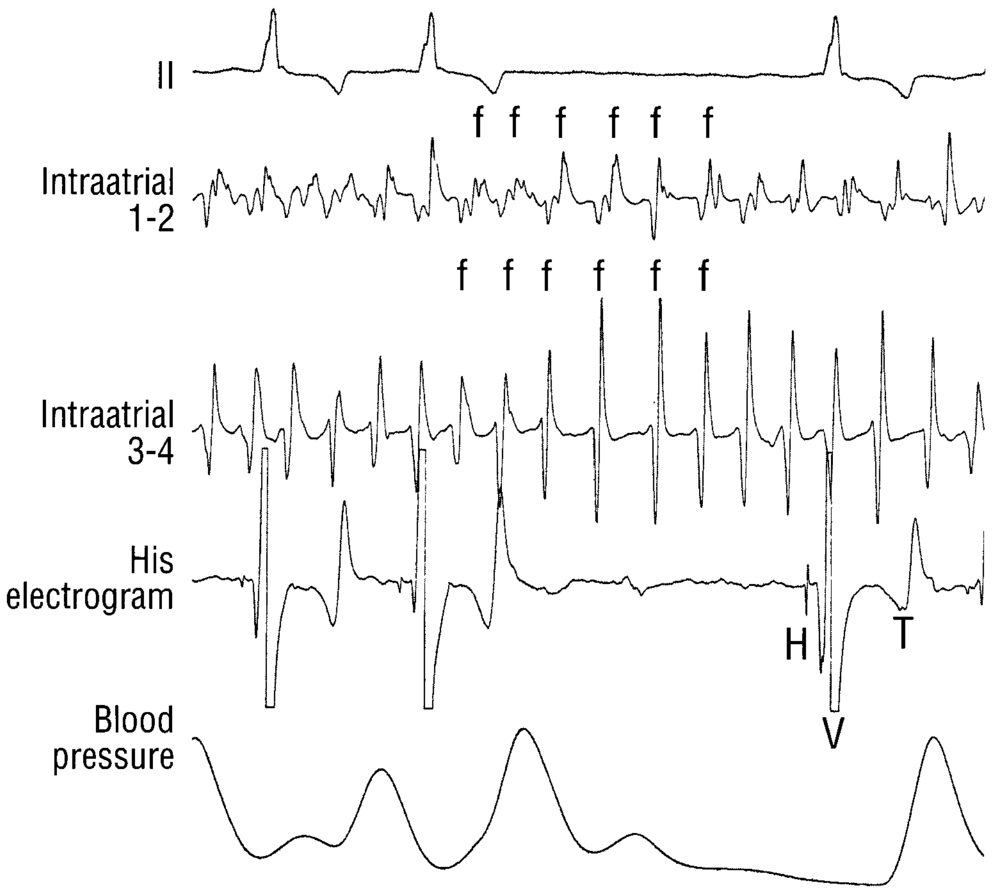


FIGURE 18–12

Electrophysiologic recordings from a dog with atrial fibrillation. A quadripolar catheter was positioned in the right atrium. The more distal poles of the catheter (1–2) show electrograms of the f-waves, which are more fragmented than those recorded between poles 3 and 4. The His electrogram shows a deflection for the depolarization of the bundle of His (*H*), confirming the supraventricular origin of the arrhythmia. The interval between f-waves varied between 120 and 80 msec or 545 and 750 beats/min, yet the ventricular response varied between 800 and 300 msec or 80 and 200 beats/min. *V*, ventricular depolarization; *T*, ventricular repolarization. Paper speed 100 mm/sec.

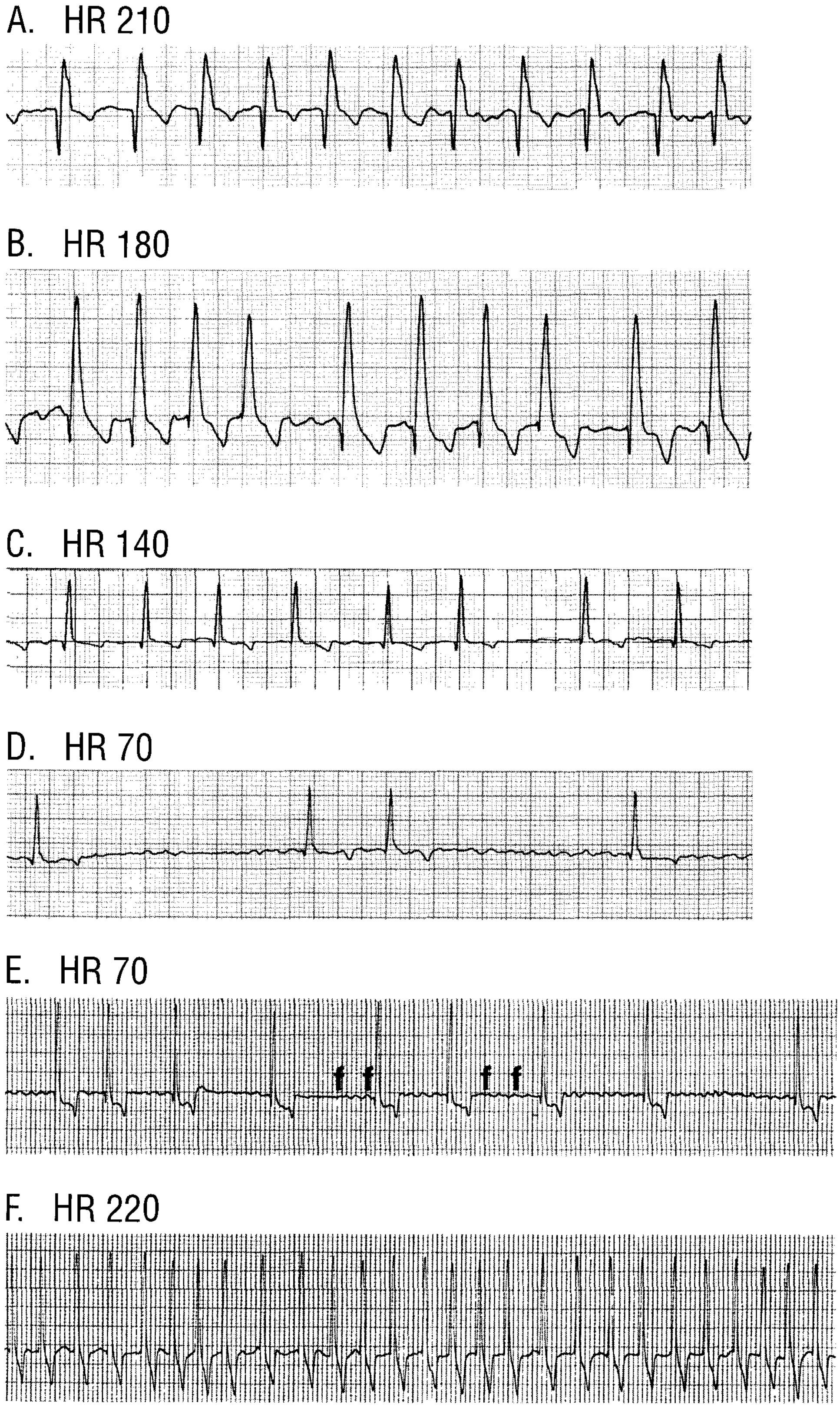


FIGURE 18–13

The ventricular response rate during atrial fibrillation depends on the integrity of the AV node, number of wavelets, degree of concealed conduction, and balance between sympathetic and parasympathetic tone. Paper speed 50 mm/sec (except (E) and (F), 25 mm/sec), 1 mV = 1 cm. (A) Lead II from a Doberman pinscher with dilated cardiomyopathy (DCM). In addition to the rapid rate, notice the prominent Q waves and widened R wave that is not tall. These are characteristic of Doberman DCM. (B) Lead II from a 12-year-old mixed dog with severe tricuspid and mitral regurgitation. The QRS complexes are wide, reflecting left heart enlargement due to chronic mitral regurgitation. (C) Lead II from a 12-year-old Dachshund with mitral regurgitation. The rhythm is not as distinctly irregular as that in (B) and may even be confused with a sinus arrhythmia. In cases such as this it is important to examine all leads, including precordial leads, for P waves. (D) Lead II from a 7-year-old, anemic collie. Although atrial fibrillation is present, the slow ventricular response rate negates treatment to decrease AV nodal conduction. (E and F) Lead II from a golden retriever with subaortic stenosis, mitral regurgitation, and chronic atrial fibrillation. During a catheterization procedure the dog became extremely bradycardic, with periods of ventricular asystole lasting 5 seconds (E) (f = fibrillation waves). Epinephrine was administered, and the ventricular response rate increased drastically (F), illustrating the effect of catecholamines on AV nodal conduction. When the rate is fast, the irregularity of the rhythm appears less.

AUTONOMIC INFLUENCE. Increased sympathetic or parasympathetic tone can provoke AF.[62–65] Both shorten the refractory period, which can potentiate re-entry;[62] vagal stimulation also causes unequal shortening of atrial refractoriness, which creates electrophysiologic heterogeneity.[63] Vagally induced AF can occur in dogs anesthetized with narcotics without premedication with vagolytic drugs. In dogs with diseases that may have simultaneous elevations in both parasympathetic and sympathetic tone (e.g., pain and stress of gastric torsion), the vulnerability to AF is increased.

ATRIAL STRETCH. Volume overload stretches the atria, and this contributes to the ability to initiate and sustain AF;[63, 66] the effective refractory period is increased more in thin areas (versus thicker regions such as the pectinate muscles) and contributes to *dispersion of refractoriness* (greater heterogeneity). This is important in re-entrant arrhythmias.

NUMBER OF WAVELETS. One hypothesis for the mechanism of AF involves multiple re-entrant circuits (the multiple wavelet theory[67–71]). Recently, this theory has been challenged, and the hypothesis of a single source coupled with a changing wavefront has been proposed (José Jalife, 1998, personal communication). For AF to be perpetuated, a minimum of 6 wavelets must be propagating at any one time.[71] The number of wavelets that can exist in the atria and the propensity for AF are determined by both the size of the atria (critical mass) related to the size of the conduction block and the wavelength. The atrial refractory periods tend to increase with body size (e.g., rabbit: 70 msec;[75] horse: 200 msec[76–78]). As the size of the animal increases, so does the wavelength, and the most important determinant is the refractory period.[78] The longer the wavelength, the fewer the wavelets, and vice versa. Normal giant-breed dogs are at the threshold for maintaining AF with the minimum number of 6 wavelets. Both increased vagal[79] and sympathetic tone shorten the wavelength and increase the likelihood for AF. In the dog, a wavelength of 8 cm is the critical length for the induction of AF.[73]

The number of wavelets may have a correlation to the surface ECG description of coarse and fine fibrillation (coarse AF is usually correlated with a more organized pattern of re-entry of the right atrium). This may relate to the ability to convert AF to a sinus rhythm.[60, 80–82]

ELECTRICAL REMODELING. Atrial fibrillation begets AF[83–86] owing to pathologic changes known as electrical remodeling. As a physiologic adaptation to the elevated heart rate, the atrial refractory period shortens by change in the composition of ion channels responsible for repolarization. Once conversion of AF to sinus rhythm occurs, this electrical remodeling does not instantly reverse, and a return of AF is more likely immediately following conversion.

PATHOLOGY. Structural and electrophysiologic changes in the atrial myocardium develop as a direct result of AF. Consequently, there is a temporal importance to converting AF when possible. Pathologic studies demonstrate degenerative atrial changes in long-term versus short-term AF.[85] These changes may not be appreciated with routine histopathologic examination. However, transmission electron micrographs of atrial myocardium from dogs with AF demonstrate mitochondrial swelling and a decreased density and organization of the cristae. These changes are characteristic of cytosolic calcium overload and are experimentally prevented with verapamil.[86, 87] Other pathologic changes with long-standing AF include fibrosis, myocytolysis, cellular hypertrophy, and alterations in gap junctions.[88]

AV NODAL CONDUCTION. The ventricular response to AF depends on the number of wavelets and the integrity of the AV node. Only a portion of the electrical activity of the atria reaches the ventricle; however, the ventricular response rate is still excessive and can result in damage to the ventricular myocardium. Impulses enter the AV node, but many penetrate only partially. This partial penetration results in varying degrees of AV nodal block. The mechanism for the AV nodal block is electrotonic inhibition and resulting *concealed conduction.* The pattern of successful penetration is random, although recent studies indicate some deterministic behavior.[89]

EFFECT OF VAGAL MANEUVERS, DRUG INTERVENTIONS. Holter recordings from dogs with AF demonstrate increased ventricular rate with exercise and excitement, and decreased rate during sleep. Also, the ventricular rate slows with expiration and increases with inspiration. Depending on the individual baseline sympathetic tone, carotid sinus massage may decrease the ventricular response rate. Drugs that slow AV nodal conduction decrease the ventricular response rate, although combination drug therapy may be required. Treatment to convert the AF in selected cases may be accomplished with cardioversion or class Ia, class Ic, or class III antiarrhythmics.

AV NODE DEPENDENT SUPRAVENTRICULAR TACHYCARDIAS

AV NODAL RE-ENTRANT TACHYCARDIA

DEFINITION, ECG FEATURES. The re-entrant circle is confined within the AV node.[30] Usually the P waves are not visible during the tachycardia because the retrograde depolarization of the atria is occurring at about the same time as the depolarization of the ventricles. If P waves are seen, they are most frequently negative in polarity in leads II, III, and aVF.[90, 91] Because this is a re-entrant tachycardia, it is paroxysmal, without a warm-up or gradual slow-down at the time of termination. The R-R intervals are usually constant.

MECHANISMS. The mechanism involves two different pathways in the AV node to conduct an impulse to the ventricle.[92] The slow (alpha) pathway conducts impulses slowly but has a shorter effective refractory period than the fast (beta) pathway, which conducts more rapidly (Fig. 18–14).[30]

With dual AV nodal physiology, AV conduction usually traverses the preferred fast pathway. However, if a premature supraventricular complex occurs, conduction travels down the slow pathway because it has the relatively shorter effective refractory period. This may be seen on the ECG as a prolonged P-R interval at the beginning of the tachycardia. Because conduction is slow, the fast pathway has time to

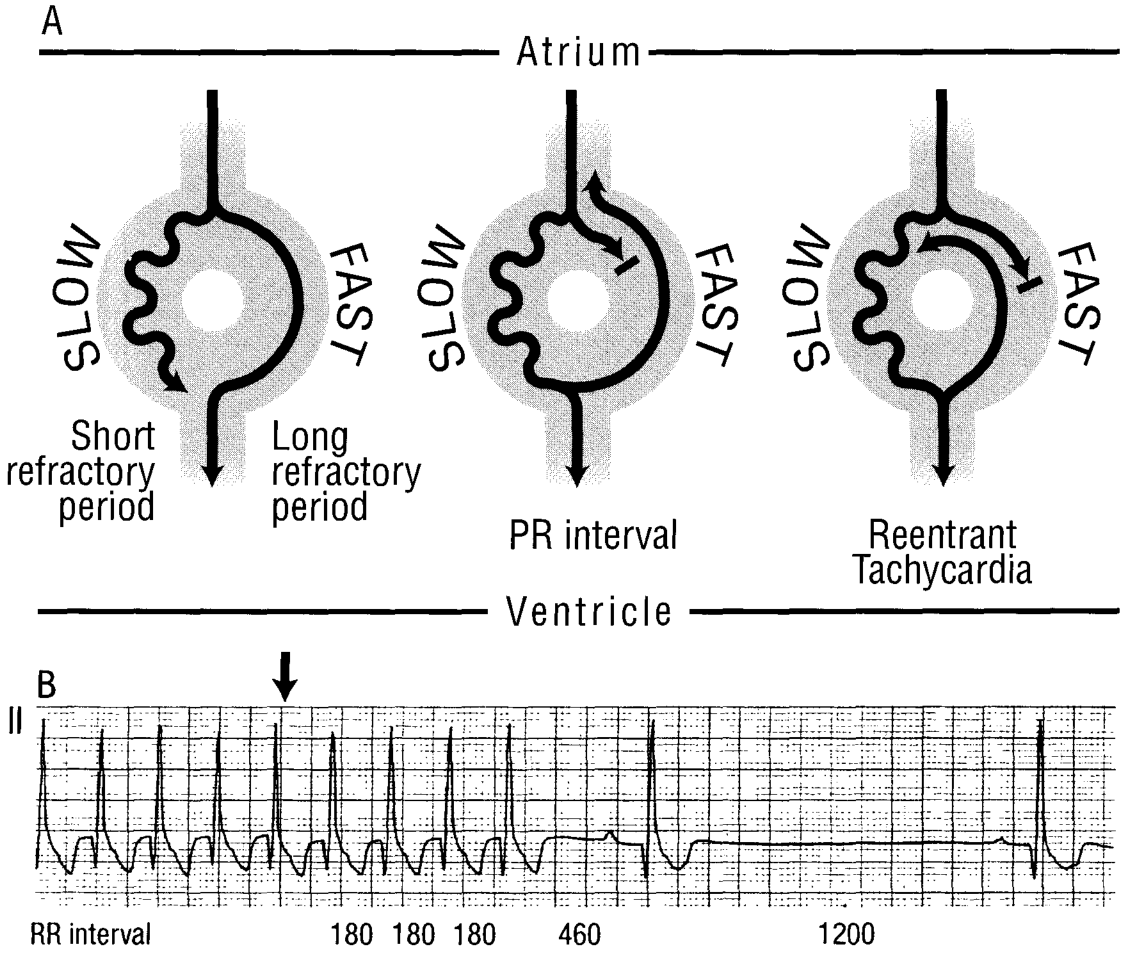


FIGURE 18–14

AV nodal re-entrant tachycardia. (A) Diagram illustrating dual AV node physiology that can support AV nodal re-entrant tachycardia. A premature atrial complex enters the AV node during the time that the fast pathway is still refractory. This results in conduction to the ventricles in the slow pathway with the shorter refractory pathway, and in a prolonged P-R interval in the initiating complex of the tachycardia. Because the slow pathway can recover, it is able to re-excite when the depolarization returns after traveling retrograde up the fast pathway. The tachycardia most commonly propagates retrogradely (depolarization wave toward the atria) up the fast pathway and antegradely (depolarization toward the ventricle) down the slow pathway. Atypical AV nodal re-entry has a depolarization pathway that travels in the opposite direction. (B) ECG recorded from a boxer with typical AV nodal re-entrant tachycardia. P waves were not seen, and carotid sinus massage *(initiated at the arrow)* abruptly terminated the regular tachycardia suddenly without a gradual slowing. The resulting sinus rate is slow because of overdrive suppression of the sinus node. Paper speed 50 mm/sec, 1 mV = 1 cm, lead II.

recover and is no longer refractory; retrograde conduction can occur, which allows the impulse to re-enter the AV node repeatedly and retrogradely depolarize the atria causing tachycardia (Fig. 18–14). If the re-entry loop is antegrade (depolarization toward the ventricles) down the fast pathway and retrograde up the slow pathway, negative P waves with a short P-R interval are seen. The R-P interval is longer than the P-R interval in this type of tachycardia.[92]

EFFECT OF VAGAL MANEUVERS, DRUG INTERVENTIONS. Vagal maneuvers or drugs, such as calcium channel blockers, β-blockers, or digitalis that increase the refractory period and decrease conduction velocity in the AV node, can terminate the re-entrant arrhythmia. If the tachycardia terminates with a P wave, AV nodal re-entrant tachycardia can be suspected, although termination can occur without the AV block. It is important to note that typical AV nodal re-entrant tachycardia does not have visible P waves except for a single one at the termination of the tachycardia without QRS complexes.

AUTOMATIC JUNCTIONAL TACHYCARDIA

DEFINITION, ECG FEATURES, MECHANISMS. Automatic junctional tachycardia, also known as ectopic junctional tachycardia, originates from tissue in the AV

nodal area (see Fig. 18–6). Because of this focus of origin, the P waves in leads II, III, and aVF are negative and frequently hidden in the QRS-T complex. Although the negative P waves may also follow or come just before the QRS complex, it is rare for junctional tachycardias to have negative P waves with a normal to long P-R interval. The latter is more likely to represent a coronary sinus rhythm (see Fig. 18–5) and is not of concern.[93] Automatic junctional tachycardias characteristically have a gradual onset and offset, and in the dog can be irregular and influenced by vagal tone.

BYPASS TRACT–MEDIATED MACRORE-ENTRANT TACHYCARDIA

A type of SVT that does not have a pathway confined above the ventricular tissue is bypass tract–mediated macrore-entrant tachycardia. This type of SVT in the dog is either uncommon or inadequately recognized, although a few reports have been made.[94–96] Bypass tracts, or accessory pathways, are embryonic muscular remnants that allow conduction from the supraventricular tissues to the ventricular tissues without traversing the normal sequence of tissues in the AV node.[97] Depending on the location and direction of conduction, pre-excitation may result in a short P-R interval and delta waves. *Delta waves* appear as notches in or slurring of the onset of the QRS complex and may cause the latter to prolong. The direction of the delta waves and the QRS complex depends on the location of the bypass tract.

THERAPY

ROLE OF TRIGGERS AND MODULATORS

Arrhythmias are dependent upon a substrate, trigger, and modulating factors.[98, 99] The *substrate* (disease) is the structural or physiologic abnormality that provides the mechanism for the arrhythmia. The substrate for a re-entry arrhythmia might be a region of damaged tissue that allows slow conduction, whereas the substrate for a triggered arrhythmia might be an abnormality in a specific potassium channel that allows the action potential duration to prolong. Although the substrate exists, it may not cause an arrhythmia unless conditions are suitable.

The *trigger* is the event that causes the induction of the arrhythmia. The trigger for SVT might be a single premature complex or an abrupt change in heart rate that sets the conditions for arrhythmia conduction. Changes in heart rate might allow early afterdepolarizations with bradycardias or delayed afterdepolarizations with tachycardias to be manifested.[62]

In addition, *modulating factors* also determine whether the arrhythmia will develop. These include catecholamines, ischemia, electrolyte changes, or alterations in autonomic tone. That is, the substrate can exist, the trigger can occur, but the arrhythmia may not begin or perpetuate if the modulating factors are not conducive. Thus, even when a specific antiarrhythmic drug is used, the effect can be overridden under certain conditions.

REASONS TO CONSIDER ANTIARRHYTHMIC THERAPY

Clear standards for drug therapy are lacking. In general, supraventricular tachyarrhythmias are treated when the dog displays associated clinical signs, when the arrhythmia causes hemodynamic instability, or when the risk for the arrhythmia to degenerate into a fatal rhythm is high.

CLINICAL SIGNS

In humans with arrhythmias, complaints of palpitations, dizziness, lightheadedness, or pain are reported.[100] In dogs, we are not aware of consequences of an arrhythmia unless syncope, weakness, or dyspnea is manifested. Detection of an arrhythmia before clinical signs develop depends on careful physical examination and ECG documentation. Dogs with SVT that have structural and functional cardiac disease will have more severe signs than those with a primary arrhythmia or minimal cardiac pathology.

HEMODYNAMIC COMPROMISE

Occasional premature supraventricular complexes or short bursts of SVT are not of clinical importance, but sustained SVT can have detrimental consequences. The hemodynamic effects depend on underlying disease, ventricular rate, and whether the dog is at rest or exercising. Sustained SVT will have more devastating results than nonsustained runs that last less than 8 to 10 seconds. Rapid ventricular rates associated with SVT reduce cardiac output, systemic blood pressure, and coronary artery perfusion. Coronary blood flow is reduced because of the shortened diastolic interval and the lower aortic perfusion pressure.[100]

Chronic, excessive elevation in the ventricular rate can result in myocardial failure known as tachycardiomyopathy.[101] Myocardial failure in the dog will result if the ventricular rate is maintained at 250 beats/min for 3 to 4 weeks.[102, 103] Such high heart rates cause biventricular enlargement and complex anatomic

changes, in addition to electrophysiologic alterations (i.e., reduced resting membrane potential). If the elevated heart rate is controlled in a relatively short time (few weeks), the myocardial failure is reversible. Cardiac output is reduced in specific SVT rhythms like AF that do not have sequential atrial and ventricular systole. In AF, the loss of atrial systole (atrial kick) reduces stroke volume approximately 20% at rest but less during exercise.[104–107]

RISK OF SUDDEN DEATH

Supraventricular tachycardia with rapid ventricular rates can cause hypotension, collapse, and death. However, the death may not be as sudden as that which results from degeneration of a ventricular tachyarrhythmia into ventricular fibrillation or ventricular asystole. Rapid SVTs may increase the liability to ventricular arrhythmias because of the associated increases in circulating catecholamines and myocardial ischemia. Moreover, long-standing SVT can lead to myocardial failure, which then leads to death.

GOALS AND CRITERIA FOR SUCCESSFUL THERAPY

Treatment goals include correction of underlying disease (ideal but often not possible); return of hemodynamic stability; conversion of the arrhythmia; or control of ventricular response rate. However, biochemical alterations (hypokalemia, azotemia, acidosis, hypoxia) can be corrected and will improve the potential antiarrhythmic effects of drugs. Diminution of clinical signs with a return of hemodynamic stability can be achieved with conversion of the SVT to a sinus rhythm, decreasing the ventricular rate, or preventing recurrence.

The desired (target) ventricular heart rate will vary with the size of the dog and the underlying cardiac disease. The heart rate taken at the veterinary hospital is generally higher than that recorded at home. As a general guideline, the desired target ventricular rate recorded in the veterinary office is approximately 100 to 140 beats/min. The heart rate at home will vary with activity level; at rest, rates as low as 60 beats/min may be recorded.

With intermittent SVT, therapeutic goals are to decrease the frequency of arrhythmia recurrence and to control the ventricular response rate during episodes of arrhythmias. Ascertaining treatment response may be difficult unless clinical signs are obvious and correlate with the recorded tachyarrhythmia, or unless repeated Holter recordings are performed.

SELECTION OF ANTIARRHYTHMIC DRUG

Supraventricular tachyarrhythmias may be divided into groups based on mechanism of arrhythmia. Although the specific mechanism may not be known, the arrhythmia can usually be grouped into a general category that will assist treatment strategy. Categorization is based on ECG characteristics and response of the rhythm to either vagal maneuvers or drug trials (described earlier). Ventricular rates greater than 250 beats/min should be considered critical and usually require aggressive IV drug therapy, with the primary goal of decreasing the ventricular heart rate. Specific treatment for sinus tachycardia is not discussed since therapy for the underlying disease usually controls the rate.

THERAPY OF SPECIFIC ARRHYTHMIAS

AV NODE INDEPENDENT (EXCLUDING SINOATRIAL NODE RE-ENTRY TACHYCARDIA)

Frequently, AV node independent tachycardias are more difficult to convert to sinus rhythm than those due to AV nodal re-entry;[36–38, 108] therefore, the goal is usually to control the ventricular response rate (Figs. 18–8, 18–15). Treatment with digoxin, calcium channel blockers,[109–114] or β-adrenergic blockers[115] is usually selected.

Acute (Intravenous) Antiarrhythmic Drug Therapy

Carotid sinus massage should always be attempted initially, and after each drug intervention. The two most commonly used calcium channel blockers are diltiazem and verapamil.[109–114]

Diltiazem has been used most commonly (0.1 to 0.3 mg/kg), administered in IV boluses of 0.05 to 0.2 mg/kg every 5 minutes to effect (Fig. 18–15). Verapamil has been used by some clinicians[116] (0.05 to 0.15 mg/kg), administered in 0.05-mg/kg boluses spaced 5 minutes apart. Calcium channel blockers have a use-dependent action on AV nodal conduction that leads to greater therapeutic effects at faster heart rates.[117] Clinical differences between verapamil and diltiazem are minimal, although diltiazem may exert a less negative inotropic effect[118–120] and have less interaction with digoxin.[121–123] It can be given as an infusion after bolus injection (5 to 15 mg/kg/hr).[124]

Beta-adrenergic blockers can be used initially or if there is inadequate control of heart rate after calcium channel blocker administration.[124a] Esmolol is an effective, ultrashort-acting β-adrenergic blocker. It is dosed at 0.1 to 0.5 mg/kg/min for 1 minute, followed by a maintenance infusion of 0.05 to 0.2 mg/kg/min. Alternatively, propranolol boluses can be administered (0.02 to 0.05 mg/kg IV) in 2-minute increments until the ventricular rate is controlled. Occasionally, healthy dogs with normal myocardial contractility may require

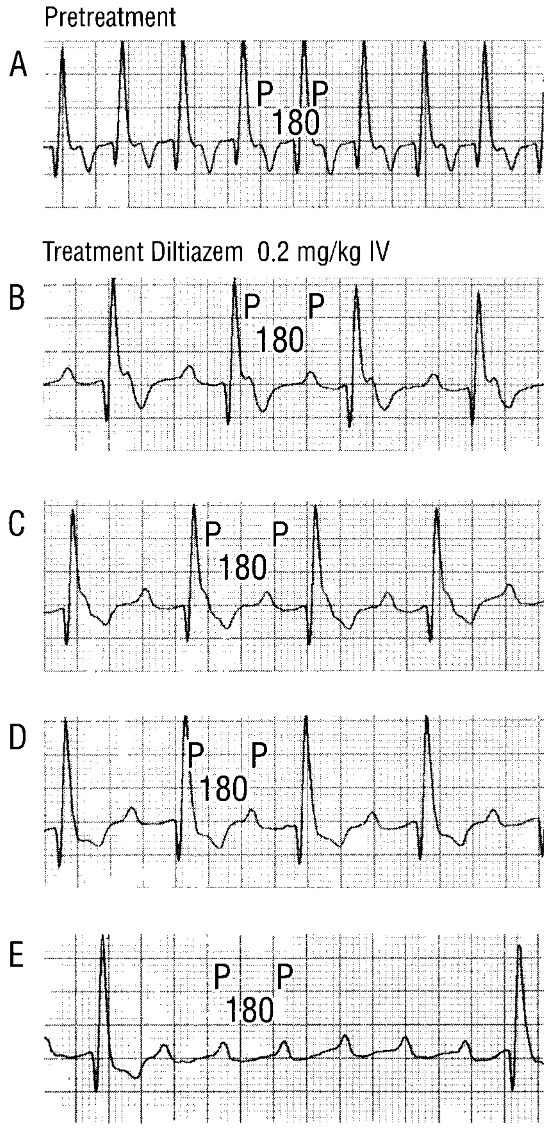


FIGURE 18–15

Lead II ECGs from a mixed-breed dog. Paper speed 50 mm/sec, 1 mV = 1 cm. (A) Initial recording reveals supraventricular tachycardia with 1:1 AV nodal conduction and heart rate of 330 beats/min. The P waves *(P)* are hidden in the T waves, but some irregularity in the ST segment suggests their presence. (B–E) Excerpts from a continuous ECG recorded over a 10-minute period. (B) Approximately 1.5 minutes after administration of 0.2 mg/kg of diltiazem (IV bolus), the P-P interval remains at 180 msec, but AV nodal conduction decreased to 2:1. (C and D) The same 2:1 conduction is present, but there is a progressive increase in the P-R interval. The P waves *(P)* are relatively obscured within the R waves. (E) Advanced AV nodal block has developed as evidenced by numerous nonconducted P waves. This dog was later treated successfully with oral diltiazem.

much higher doses to control heart rate, particularly when β-blockers are used as monotherapy. Accordingly, boluses of 0.1 to 0.3 mg/kg have been well tolerated in many cases. However, care should be taken when administering β-blockers to animals with poor contractility or hypotension. In these cases, esmolol is advantageous because of its short elimination half-life (9 minutes) compared with propranolol.[125] However, propranolol is currently inexpensive compared with esmolol, and studies in humans have shown that it produces less hypotension.

When dogs with SVT do not adequately respond to monotherapy using upwardly titrated doses of calcium channel or β-adrenergic blockers, they may be combined. Low doses of the second agent may be carefully administered (Fig. 18–16).[126] As a third-line drug for refractory SVT, edrophonium chloride, an anticholinesterase agent, may be judiciously administered as a slow IV bolus (0.05 to 0.1 mg/kg) (Fig. 18–17). Edrophonium can cause nicotinic and muscarinic side effects (vomiting, muscle twitching).[23] In addition, phenylephrine, given at 0.005 to 0.01 mg/kg IV, can slow AV nodal conduction of SVT. Phenylephrine is an α_1-adrenergic agonist that causes arterial vasoconstriction and resultant systemic hypertension. This increased pressure will reflexly, via baroreceptor stimulation, increase vagal tone, slow AV nodal conduction, and reduce the ventricular response rate.

Although IV digoxin has historically been used to treat SVT, its acute benefit is limited because the onset of action is slow,[119, 127] and occasional ST segment depression is seen after treatment.[128] The primary effect of digoxin is a central and peripheral enhancement of vagal tone;[129] thus, with a high sympathetic tone in a distressed animal, other or additional therapy (calcium channel or β-adrenergic blockade) may be advantageous. Digoxin does have a parasympathomimetic effect when administered orally, but IV administration increases central sympathetic outflow.

Adenosine is used in humans to diagnose and acutely treat SVT, primarily because of its effect on the AV node (attenuation of the inward calcium current).[130] Diagnostically, if the SVT continues after adenosine administration but the ventricular response rate slows, AV nodal re-entry is unlikely and AV nodal independent SVT is probably present. Triggered atrial tachycardia can be abolished with adenosine, perhaps because of its abbreviation of the action potential caused by activation of outward potassium current in atrial tissue. Its short half-life (less than 10 seconds[130, 131]), limits adverse side effects. Although adenosine has been studied extensively in the dog,[130–136] the need to deliver it extremely rapidly through a large vein, and its high cost, have curbed its use.

Chronic (Oral) Antiarrhythmic Drug Therapy

Acute therapy may be followed by chronic oral drug administration in some cases to (1) slow AV nodal conduction when treating AV node independent SVT, or (2) convert AV nodal re-entrant SVT to sinus rhythm. These agents include diltiazem (1 to 3 mg/kg tid); verapamil (1 to 3 mg/kg tid); atenolol (0.5 to 1 mg/kg sid to bid); propranolol (0.3 to 1.5 mg/kg tid);

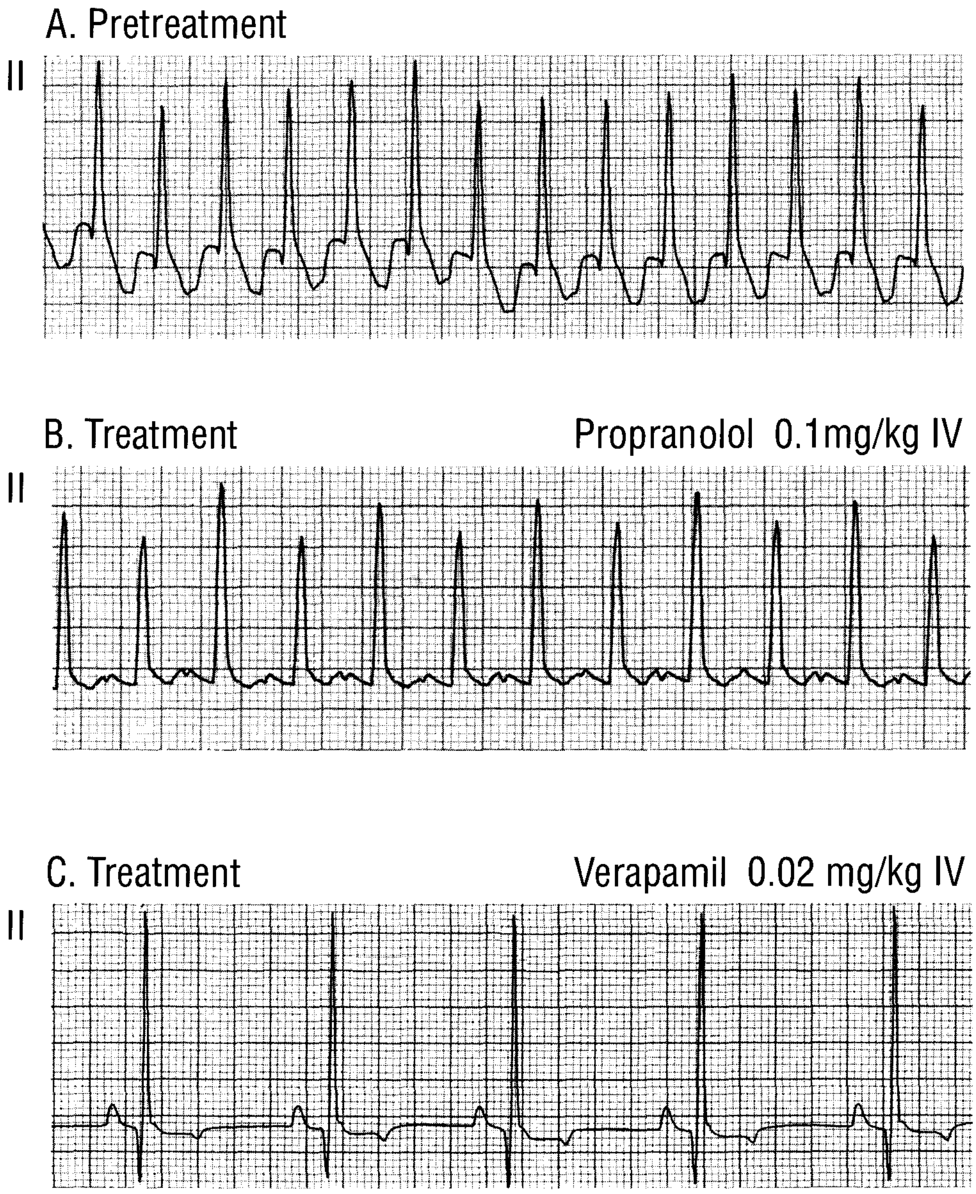


FIGURE 18–16

ECG from a 6-month-old Labrador retriever that was found moribund after being unloaded from an airplane. Paper speed 50 mm/sec, 1 mV = 1 cm, lead II. (A) The heart rate was initially 300 beats/min and P waves were not visible. Neither vagal maneuvers nor shock therapy improved the ECG. (B) Propranolol was administered (0.1 mg/kg IV) with minimal effect on heart rate. Electrical alternans developed coincident with this therapy. (C) Verapamil was administered (0.02 mg/kg IV), which abruptly terminated the tachycardia. Sinus rhythm was resumed and no further treatment was needed.

and digoxin (0.005 to 0.01 mg/kg bid). These drugs may occasionally convert the arrhythmia to sinus rhythm, but other agents have been used for the specific goal of conversion or prevention of AV node independent SVT. These include procainamide (10 to 20 mg/kg tid to qid); quinidine (10 to 20 mg/kg tid to qid); propafenone (3 to 4 mg/kg tid); flecainide (1 to 5 mg/kg bid to tid); sotalol (0.5 to 2 mg/kg bid to tid); or amiodarone (loading dose 10 mg/kg for 7 days, then 5 mg/kg q 24 to 48 hr).

The efficacy of chronic oral medication is sometimes suboptimal for several reasons. An oral formulation may not have comparable efficacy to IV preparations and adjustments may be needed.[137] Lack of response may be due to inadequate dosage, or combination drug therapy may be required.[138] The use of calcium channel blockers and β-adrenergic blockers, or digoxin plus either of these two agents, may provide better antiarrhythmic control in some cases. The dosage of each drug is usually decreased to reduce untoward effects when combination therapy is used. Long-acting or sustained-release preparations can sometimes be beneficial when treatment compliance is an issue. As a general rule, the same total dose (mg/kg) that would be given in a 24-hour period (e.g., 2 mg/kg tid) is applied to the sustained-release formulation when administered once daily (e.g., 6 mg/kg/day).

Ectopic atrial tachycardias may occasionally be converted to sinus rhythm or controlled with class Ia, class Ic,[139–142] or class III drugs (see chapter 17, Table 17–2). The latter two classes are considered more effective.[143] Some class Ic and class III drugs also affect AV nodal conduction owing to their β-adrenergic blocking properties. Currently, the most effective drugs used for

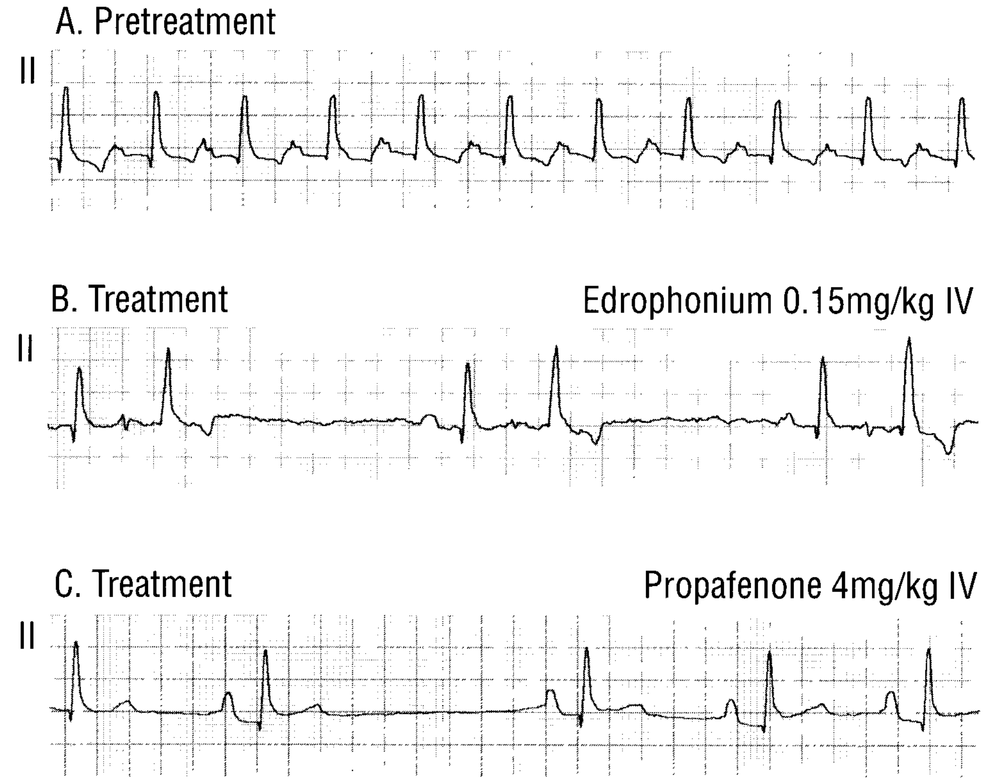


FIGURE 18–17

ECG from a dog with supraventricular tachycardia. Paper speed 50 mm/sec, 1 mV = 1 cm, lead II. (A) Initial ECG reveals rapid, narrow, and regular supraventricular tachycardia. (B) Treatment with edrophonium (0.15 mg/kg IV) quickly terminated the tachycardia, but premature extrasystoles persisted. (C) Long-term treatment with propafenone (4 mg/kg IV) successfully suppressed the supraventricular tachycardia. Initially, treatment with diltiazem and atenolol were tried but were ineffectual as monotherapy or in combination.

ectopic atrial tachycardias in humans are propafenone, flecainide, sotalol, and amiodarone.[144] Ectopic junctional tachycardias have been somewhat effectively treated with amiodarone.[143] Unfortunately, clinical studies evaluating the effectiveness of these agents are lacking in dogs.

ADVERSE EFFECTS. Excessive bradycardia may occur with calcium channel or β-adrenergic blockade because of the effect on the sinus or AV node. These drugs may also cause hypotension, particularly when administered IV (Fig. 18–18). If severe bradycardia results in hypotension, cardiovascular support may require IV fluids: atropine (0.02 to 0.04 mg/kg tid to qid, IV, IM, or SC) or glycopyrrolate (0.005 to 0.01 mg/kg IV, IM, or SC), or isoproterenol (0.04 to 0.08 μg/kg/min IV or to effect).

Cessation of chronic β-blocker therapy should be gradual. Sudden withdrawal may result in catecholamine sensitivity because of drug-related increase in β-adrenergic receptors and up-regulation associated with β-adrenergic blockade.[145, 146] Calcium channel blockers

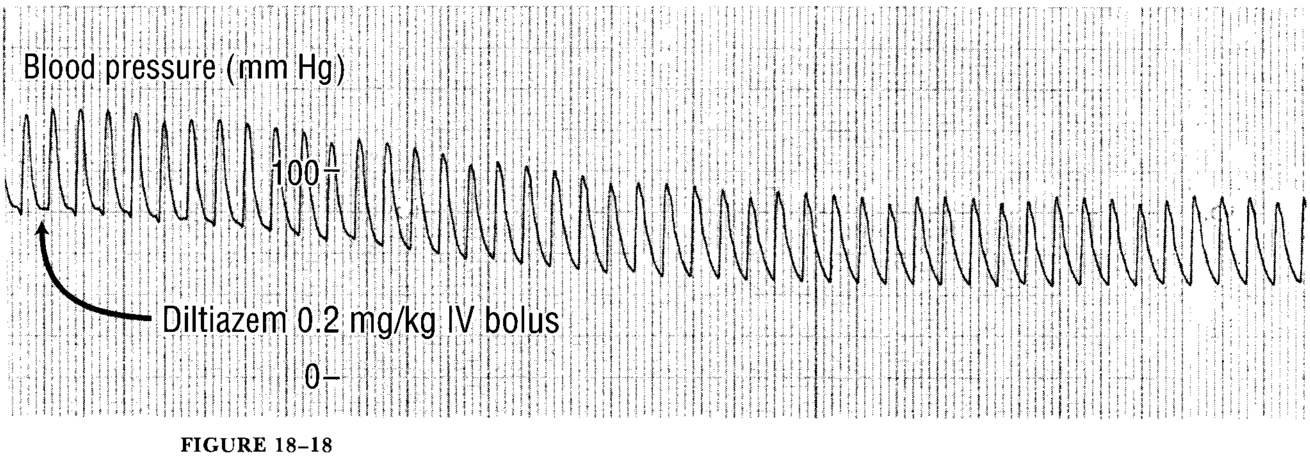


FIGURE 18–18

Arterial blood pressure recorded during IV bolus administration of diltiazem (0.2 mg/kg). The hypotensive effect of calcium channel blockade is evident as the blood pressure drops from 130/80 mmHg to 85/45 mmHg. This effect can be more profound with verapamil. Thus, to avoid hypotension, calcium channel blockers should be administered IV slowly.

and, particularly, β-adrenergic blockers may cause dose-related negative inotropic effects, which should be considered in animals with myocardial failure.

Digoxin toxicity most commonly causes depression, anorexia, and diarrhea, although ECG evidence of prolonged AV nodal conduction (P-R interval prolongation) or arrhythmias can also occur. If digoxin toxicity is suspected, the drug should be stopped for at least 48 hours; if continued treatment is needed, the dose is empirically reduced by half. Determination of digoxin serum levels (drawn 8 to 12 hours after administration) is required to confirm toxicity and adjust dosage.

ATRIAL FLUTTER AND ATRIAL FIBRILLATION

Atrial fibrillation is usually a chronic, permanent canine arrhythmia associated with severe atrial dilation due to dilated cardiomyopathy or volume overload (e.g., mitral regurgitation, uncorrected patent ductus arteriosus). Occasionally, acute onset of AF or paroxysmal (intermittent) AF is detected. In the former, one looks to control the ventricular response rate, while in the latter, the goal is conversion to a sinus rhythm or prevention of episodic AF. Atrial flutter usually progresses to AF, and principles of therapy are similar.

Control of Ventricular Response Rate

CLINICAL EVALUATION. In most dogs with AF, conversion to sinus rhythm is not an obtainable goal. The ventricular rate will vary from 120 to 320 beats/min depending on the type of AF and concealed conduction, the integrity of the AV node, and the level of autonomic tone. Heart rate reduction to a single optimal level cannot be universally stated when treating atrial fibrillation, and it varies with each animal. Ideally, a 24-hour Holter recording will give the clearest appreciation of heart rate and rhythm during rest and activity. Clients can often be trained to monitor and record heart rates at home, and evaluation of heart rate under specific circumstances can be helpful, including (1) in-hospital auscultated resting rate, (2) in-hospital auscultated rate following minimal exercise, and (3) heart rate from a lead II ECG rhythm strip. Adequate heart rate control may occur over a range of 80 beats/min during rest and 150 beats/min during exercise for a large-breed dog. When slower ventricular heart rates are present (<100 beats/min), there is no need to reduce the ventricular heart rate further.

ACUTE THERAPY. The drugs and principles discussed for the short-term treatment of other SVT rhythms apply to the treatment of atrial flutter and AF. Digoxin is usually not used IV when rapid control of tachycardia is required. Instead, calcium channel blockers, β-adrenergic blockers, or both represent the first choice for IV therapy (Fig. 18–19).

CHRONIC (ORAL) THERAPY, DIGOXIN ALONE. The first choice to control heart rate in dogs with atrial flutter or AF has traditionally been digoxin (Fig. 18–20). Digoxin decreases the ventricular response (rate) by its indirect vagal effects,[147, 148] and by its actions to abbreviate atrial myocardial action potential duration and refractory period.[78, 149] The latter allows more wavelets to bombard the AV node, resulting in greater concealed conduction with fewer transmitted impulses reaching the ventricle.[150, 151] Although digoxin can effectively control the heart rate in many dogs, this control is neither universal nor optimal during exercise, stress, or excitement.[152–156] Heightened sympathetic tone during these periods results in excessive heart rate (see Fig. 18–13). Additional treatment with β-adrenergic blockers or calcium channel blockers is often necessary.

CHRONIC (ORAL) THERAPY, COMBINATION DRUGS WITH DIGOXIN. Because most dogs with AF have some degree of myocardial failure, treatment with digoxin serves a dual role. Although digoxin has previously been used alone, it is usually more effective when combined with either a β-adrenergic blocker (e.g., atenolol, propranolol, metoprolol) or a calcium channel blocker (e.g., diltiazem), both of which increase the AV node refractory period.[157–159] In humans, better results were achieved when digoxin was combined with calcium channel blockers than with β-adrenergic blockers.[160–163] In the management of AF, serum digoxin levels should be determined approximately 7 to 10 days after initiation of therapy; blood is sampled 8 to 12 hours after digoxin administration.

Conversion of Tachyarrhythmia and Prevention of Initiation

APPLIED ELECTROPHYSIOLOGIC PRINCIPLES. The multiple wavelet theory of AF has direct bearing on treatment to convert the arrhythmia or to control the ventricular response. Drugs may either increase (digitalis) or decrease (quinidine, procainamide, flecainide, propafenone, sotalol, amiodarone)[79] the number of wavelets; this frequently determines whether the drug stabilizes or converts the AF, respectively. Drugs that stabilize the AF may actually decrease the ventricular response (e.g., digoxin), whereas drugs that eventually convert the AF may initially increase the ventricular response (e.g., quinidine). The most reliable determinant of the effect of a drug on the number of wavelets is its effect on the wavelength. Other factors are important in the potential of a drug to act as an antifibrillatory agent. For example, sotalol markedly increases the wavelength and decreases the number of wavelets, but its antifibrillatory action is disappointing because of *reverse use-dependency*.[79, 164] This refers to decreased antiarrhythmic action with faster heart rates (i.e., when antiarrhythmic efficacy is needed the most). The faster the heart rate, the less antifibrillatory action because of a reduced lengthening of the action potential.[71, 165–167] This reverse use-dependence is not true for all class III antiarrhythmics. Amiodarone is effective over a wide range of

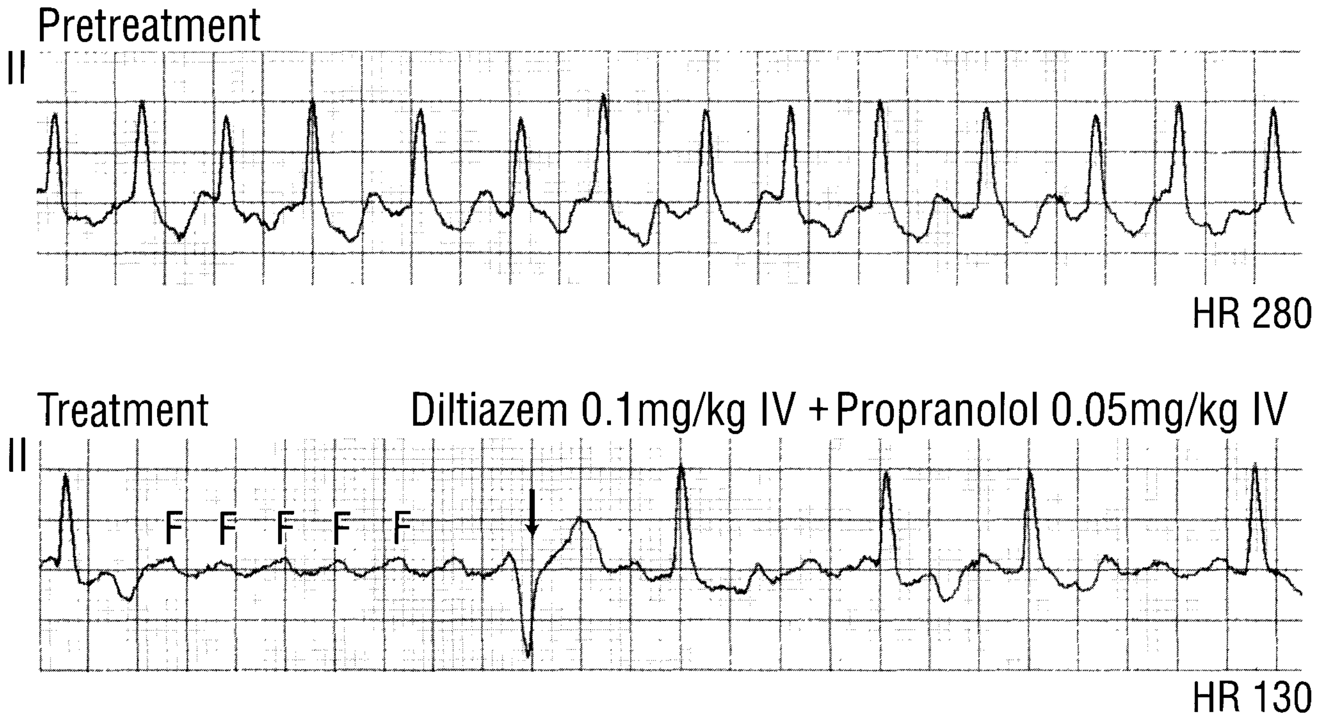
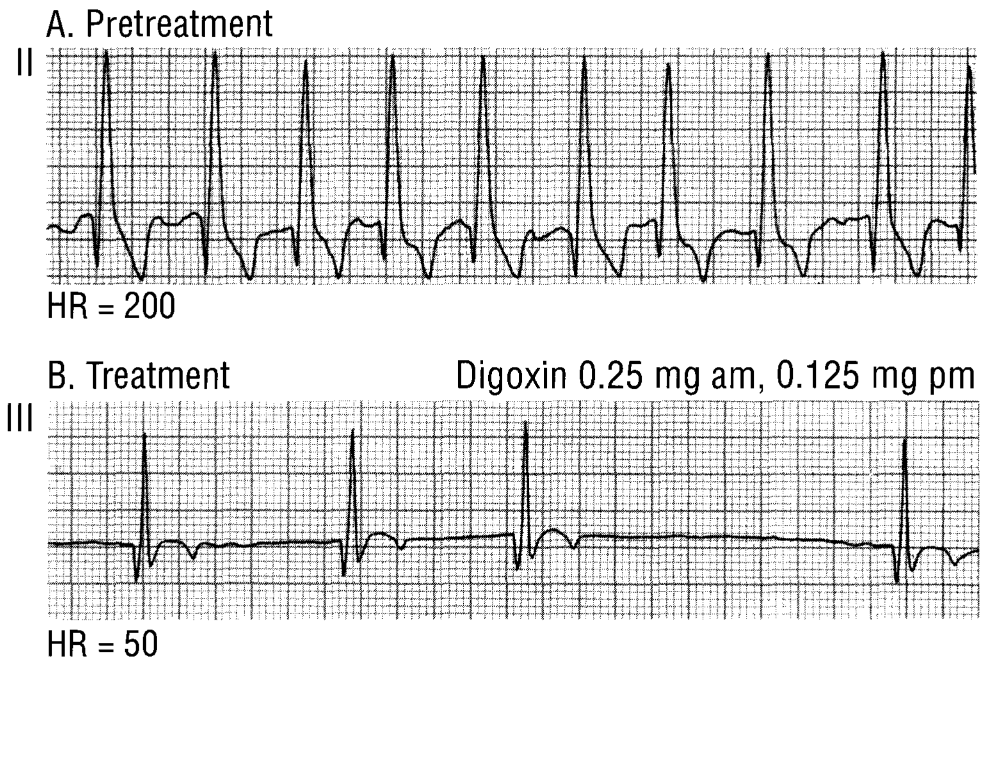


FIGURE 18-19

ECG from a dog with atrial flutter. Paper speed 50 mm/sec, 1 mV = 1 cm, lead II. *(Top)* Initial ECG revealed a rapid heart rate (280 beats/min). Treatment with diltiazem (0.1 mg/kg IV) did not alter the heart rate. The decision was then either to increase the dose of diltiazem and repeat the bolus or administer a β-adrenergic blocker. Propranolol was given. *(Bottom)* The ventricular response rate slowed shortly after administering a propranolol bolus. Caution should always be used when combining drugs that affect AV nodal conduction. The lowest effective dose should be tried first and the amount gradually increased as needed. Flutter *(F)* waves are apparent. Slowing of the AV nodal conduction (and AV block) was so pronounced that a ventricular escape complex was initiated *(arrow)*.

FIGURE 18-20

Lead II ECG from a boxer with dilated cardiomyopathy and atrial fibrillation. Paper speed 50 mm/sec, 1 mV = 1 cm. (A) Initial ECG reveals atrial fibrillation and left ventricular enlargement pattern. The ventricular response rate was rapid at 200 beats/min. (B) Control of heart rate was achieved with digoxin alone. This ECG reveals a heart rate of only 50 beats/min, slower than desired. Serum digoxin concentration was normal, a 24-hour Holter recording revealed acceptable heart rates, and the dog did well clinically.



heart rates in the treatment of AF.[168, 169] The mechanisms are not clear.

Although reduction in wavelet numbers is a major mechanism for drug action to abolish AF, drugs that can enlarge the *excitable gap* (area of recovered and excitable myocardium) in this re-entrant arrhythmia also have an important therapeutic impact. Class Ia and class Ic antiarrhythmic agents (see chapter 17, Table 17–2) can be expected to enlarge the excitable gap during AF by slowing conduction velocity.[35, 108, 170] This abolishes the re-entrant circuit and arrhythmia.

THERAPY FOR CONVERTING TACHYARRHYTHMIA. In humans and horses, conversion of AF is more common than in the dog. Most dogs with AF have enlarged atria and cardiac pathology. Occasionally, AF can develop in dogs without cardiomegaly (e.g., gastric torsion) or in apparently normal giant-breed dogs (see previous discussion). Interventions may be required if hemodynamic compromise develops or it is feared that the acute, sustained AF may become permanent. The longer AF persists, the less likely that conversion will occur[171] and the more likely that myocardial failure will result.

Quinidine has been the initial choice when conversion of AF is sought.[172] Quinidine can cause an increased ventricular response rate both because of its vagolytic effects and the decrease in concealed conduction into the AV node as the number of wavelets is decreased. As the AF becomes more organized, the ventricular response rate increases. Therefore, quinidine may need to be combined cautiously with drugs that slow AV nodal conduction, such as digoxin. Calcium channel blockers may be preferable to digoxin because of their salutary effect on atrial myocardial pathology, which develops as a result of AF.[86, 87] β-adrenergic blockers increased the effectiveness of quinidine in converting AF in one human study.[173]

Data from human trials suggest that some of the class Ic antiarrhythmics may be more effective than quinidine. Flecainide and propafenone have been used for conversion and prevention of AF,[146, 174–176] but effectiveness in dogs is unknown. In experimental canine studies, flecainide (1 to 5 mg/kg PO bid to tid) was most effective in AF potentiated by excessive vagal tone.[62, 79, 164] In humans, flecainide[177] was potentially effective for treating nonchronic AF in the absence of structural heart disease.[178, 179] Whether this application may apply to specific situations in dogs (i.e., AF in giant breeds) is not known. Very limited experience in dogs with paroxysmal AF treated with flecainide yielded a favorable response without side effects. Given the vagolytic properties of flecainide, it may be more beneficial when combined with a β-adrenergic blocker in diseased hearts.[180]

In contrast to flecainide, propafenone (3 to 4 mg/kg PO, tid) is a more effective treatment in sympathetic potentiated AF.[79] Moreover, propafenone combined with digoxin has been shown in humans to be effective.[181]

Class III drugs (see chapter 17, Table 17–2) have been used to convert and prevent AF. However, studies with experimentally induced AF in the dog have shown that the ability of sotalol to terminate AF is handicapped because of reverse use-dependence.[79] Nonetheless, it still may be successful in the prevention of AF before the heart rate has the opportunity to accelerate.[79] Amiodarone has been effective in the conversion of AF, but reversion to sinus rhythm may take weeks;[182, 183] this agent has been proposed as the most promising of the antiarrhythmic drugs for suppressing recurrent AF.[184, 185] Recent studies of ibutilide (dose in humans, 0.005 to 0.025 mg/kg IV) have shown this class III drug to be effective in cardioversion when administered IV in acute AF, and with fewer side effects than other drugs.[186] Ibutilide prolongs the action potential differently than the better-known sotalol and amiodarone. Whereas the latter prolong repolarization by blocking potassium channels, ibutilide increases the plateau phase by enhancing the slow inward depolarizing Na^+ current.[187]

TEMPORARY ATRIAL FIBRILLATION

Although AF tends to be chronic and sustained in the dog, it is temporary and self-limiting in some cases (e.g., when dogs are anesthetized with narcotics such as fentanyl citrate without pretreatment with an anticholinergic, they can spontaneously develop transient AF). Enhanced vagal tone shortens the atrial refractory period and increases the dispersion of refractoriness, both of which facilitate AF.

AV NODE DEPENDENT (INCLUDING SINOATRIAL RE-ENTRY) TACHYCARDIA

Sinus nodal and AV nodal re-entrant tachycardias can potentially be converted to sinus rhythm with drugs that affect the slow calcium channels, such as calcium channel blockers or β-adrenergic blockers. In humans with AV nodal re-entrant tachycardia, radiofrequency ablation of the slow pathway is the preferred treatment.[188, 189] At this time, antiarrhythmics represent the usual therapy in dogs.

Control of Ventricular Rate and Conversion of Arrhythmia

The AV nodal tissue is sensitive to autonomic influences. Therefore, physiologic maneuvers (see Fig. 18–7) and drugs that increase parasympathetic or decrease sympathetic tone will potentially stop re-entrant conduction. Digoxin or β-adrenergic blocking agents can be used to terminate or prevent the arrhythmia.

Agents that act directly to slow conduction in the slow pathway of the AV node, such as calcium channel blockers, will have similar antiarrhythmic effects. For acute therapy, the same principles discussed under the treatment of atrial tachycardias are true. Because the re-entrant loop can potentially be blocked in the fast pathway, class Ia, class Ic, and class III drugs (see Table 17–2) that slow conduction in fast channel cardiac muscle cells may also have antiarrhythmic benefit in AV nodal re-entrant tachycardia.[92, 142, 178, 190–192] Studies in humans have shown similar benefits when verapamil (class IV) and flecainide (class Ic) were compared.[178] In addition, propafenone, which differs from other class Ic drugs because of its additional class II (approximately 1/40th the β-adrenergic blocking potency of propranolol)[193] and class IV actions, is regarded as an effective antiarrhythmic.

SELECTED CANINE CARDIAC DISEASES WITH ARRHYTHMIAS

BYPASS TRACT MACRORE-ENTRANT TACHYCARDIA IN LABRADOR RETRIEVERS

Orthodromic (conduction through the AV node and retrograde back to the atrium via a bypass tract) reciprocating tachycardia has been identified in Labrador retrievers.[94] In one study, a bypass tract was identified as an atrioventricular posteroseptal accessory pathway.[194] It conducted only in the retrograde direction, representing a concealed accessory pathway that did not display as a pre-excitation on the ECG during sinus rhythm. The rapid rate of the SVT induced episodes of acute pulmonary edema.

Labrador retrievers also have a higher incidence of tricuspid dysplasia/Ebstein's anomaly.[195] The septal leaflet of the tricuspid valve is adhered to the interventricular septum. In humans, bypass tracts are frequently associated with Ebstein's anomaly.[97] The posterior and septal leaflets of the tricuspid valve are the last to develop in the fetus. Arrested tricuspid valve development results in remnants of muscular or specialized tissue connections (the subsequent bypass tracts) across the AV groove. In humans, the treatment of choice is radiofrequency ablation of the bypass tract, a technique that is of limited availability to veterinary medicine.

TACHYCARDIA ASSOCIATED WITH SICK SINUS SYNDROME IN MINIATURE SCHNAUZERS

Sick sinus syndrome (SSS) represents a disorder in which cardiac conducting tissues are diffusely affected. It is characterized by syncope—typically in middle-aged to older, female miniature schnauzers and occasionally, other breeds (West Highland white terrier, aged dachshunds). The cause for syncope is frequently severe bradycardia or abrupt sinus arrest (see discussion under Bradyarrhythmias). However, some dogs also have episodes of nonsinus SVT that follow a long pause as an escape tachycardia (*bradycardia-tachycardia syndrome*) or they may precede a long pause (*tachycardia-bradycardia syndrome*). The mechanism for SVT is believed to be abnormal atrial automaticity. Dogs with SSS are treated with pacemaker implantation to control the bradycardia (chapter 20). It is not recommended that the SVT be treated without pacemaker implantation because of the risk of exacerbating the bradycardia.

VENTRICULAR TACHYARRHYTHMIAS

EMERGING ROLE OF MECHANISMS IN TREATMENT DECISIONS

CLASSIFICATION OF ARRHYTHMIAS BY MECHANISM

When the mechanism of an arrhythmia is known (chapter 16)[196] or suspected, antiarrhythmic drugs may be more rationally selected.[197–199] Not all antiarrhythmic therapy is efficacious or even safe, and certain agents may increase mortality.[200–202] Knowledge of mechanisms is limited for spontaneous canine arrhythmias; new approaches to drug classification may become useful when clinical data are accumulated. For example, the Singh-Vaughan Williams antiarrhythmic drug classification[203–205] was reorganized with the aim of categorizing antiarrhythmic drugs based on their means of abolishing the underlying mechanism of VT. Referred to as the "Sicilian Gambit,"[206, 207] this scheme emphasized how drugs affect ionic currents, receptors, and pumps and the vulnerable parameter that would permit them to abolish the arrhythmia.[206] Other proposed classifications of antiarrhythmic drugs consider not only the drugs' action on a particular channel but also the pharmacokinetics[208] or the underlying heart disease.[209] The kinetics can have important implications with regard to the antiarrhythmic and proarrhythmic effects of each drug. These still require clinical study in dogs.

ROLE OF TRIGGERS AND MODULATORS

The autonomic nervous system plays an important role in arrhythmogenesis and the efficacy of drugs. Some of the more salient relationships are described here:

FIGURE 18–21

Continuous Holter recording from a boxer with syncope associated with excitement and exercise. (A) Sinus arrhythmia. (B) During excitement and exercise, the sinus heart rate accelerated. (C) Shortly after onset of the increased sinus heart rate, ventricular arrhythmias developed, including paroxysms of ventricular tachycardia (VT). Syncope occurred when runs of VT lasted more than 8 seconds. Mexiletine alone was ineffective, but treatment with atenolol and mexiletine suppressed more than 90% of the ventricular arrhythmias and abolished the syncope. The VT identified in boxers is frequently associated with the increased heart rate (exercise and excitement).

EFFECTS ON THE VENTRICULAR MYOCARDIUM. The autonomic nervous system plays a pivotal role in the initiation, characteristics, and perpetuation of most arrhythmias (Fig. 18–21).[99, 210–212] Elevations in cardiac sympathetic activity have been documented in sustained ventricular arrhythmias.[213] The sympathetic nervous system can potentiate arrhythmias caused by re-entry, automaticity, and triggered activity.[214] Sympathetic stimulation of the Na/K pump hyperpolarizes the membrane, which allows more availability of Na^+ channels. This increases conduction velocity, which under certain circumstances may increase the propensity for re-entrant arrhythmias. Moreover, catecholamines shorten repolarization and the effective refractory period. This can favor re-entrant arrhythmias by allowing more dispersion of refractoriness (see chapter 16). Catecholamines potentiate arrhythmias caused by automaticity because of an increase in the slope of phase 4 and enhancement of the slow inward current. They also promote development of delayed afterdepolarizations because they stimulate calcium current, allowing elevations of intracellular calcium. Alpha-adrenergic agonists block specific potassium currents (I_K, I_{to}) that prolong the action potential duration. Given an existing substrate, such an action will increase early afterdepolarizations.

Differences exist in the impact between the neurogenic and humoral adrenergic stimulation.[99] The neurogenic vector (norepinephrine from sympathetic nerve fibers) usually occurs suddenly, for short periods of time, and with unequal distribution to ventricular myocardium; the humoral vector (circulating epinephrine from the adrenal glands) occurs more gradually, for a longer period, and with a more generalized effect. Therefore, the influences of the sympathetic and parasympathetic systems can be complex, particularly during certain circumstances such as exercise.[210, 215] Arrhythmias also may be triggered with certain activities, including sleep,[13, 99] with changes in the sympathetic balance accompanying congestive heart failure,[216] or with hypertrophic cardiomyopathy. Not only are ventricular arrhythmias more likely under circumstances of elevated sympathetic tone, but also large sympathetic surges are generated as a result of ventricular tachycardia.[211]

EFFECTS ON ANTIARRHYTHMIC POTENTIAL. Sympathoexcitation may contribute to hemodynamic stability during VT, although under some circumstances it may be detrimental.[98, 211, 217] Neurogenic and humoral sympathetic influence not only affects generation of ventricular arrhythmias but can also modify the effectiveness of antiarrhythmic drugs.[197, 218] For example, the beneficial effects of quinidine (class Ia) can be annulled with increased sympathetic tone.[219] Similarly, mexiletine (class Ib) may be less effective unless combined with atenolol. The antiarrhythmic effects of action potential prolongation by class III drugs may be optimal only when sympathetic tone is not elevated.[220, 221] One large human trial revealed that *dl*-sotalol was an effective antiarrhythmic drug[222]; however, when *d*-sotalol was tested against placebo, more deaths occurred in the treatment group.[223, 224] Because *d*-sotalol is essentially devoid of antiadrenergic actions and is functionally a pure class III drug, the antiarrhythmic effects may be lost (less blockade of potassium current) in some situations in which sympathetic tone is increased,[165, 221] and concomitant β-adrenergic blockade may be necessary.

INDICATIONS FOR THERAPY

Treatment is based upon the assumption that therapy will (1) reduce the risk of death, (2) decrease the frequency of a dangerous arrhythmia, and (3) improve or abolish related clinical signs. Beneficial results may not always occur, and adverse effects are possible (see chapter 17, Tables 17–6, 17–8).

PREVENTION OF SUDDEN CARDIAC DEATH

Sudden cardiac death can result from ventricular fibrillation (VF), ventricular asystole, or electrical-mechanical dissociation (also called pulseless idioventricular rhythm by some investigators). It was once believed that decreasing the frequency of ventricular extrasystoles would also decrease the risk of sudden death. However, this assumption is not always true. Drugs can have antiarrhythmic effects without antifibrillatory effects and vice versa. If ventricular asystole or

electrical-mechanical dissociation is the mechanism of death, then drugs that prevent VF may not affect that outcome.

Ventricular fibrillation is a common fatal canine arrhythmia. As in the atria, the mechanism is multiple re-entrant circuits. This is more likely to occur when there is more *dispersion of refractoriness* (the differences in the refractory periods of the myocytes in different locations), which, when increased, causes unidirectional blocks and re-entry. The dispersion of refractoriness that is required for re-entry to develop is within the physiologic range in the atria and outside the physiologic range for the ventricle. Thus, AF can exist without pathology in giant-breed dogs, whereas it is rare for a normal heart to develop VF spontaneously. Rapid VT usually precedes development of VF, and this rhythm increases the inhomogeneity of conduction and refractoriness. The inhomogeneity allows a fixed re-entrant circuit to degenerate into a random circuit that leads to VF. Some drugs such as bretylium may have a greater antifibrillatory than antiarrhythmic ability.[212] At times, certain electrical stimuli such as a spontaneous premature ventricular complex or discharge from an improperly programmed pacemaker during the vulnerable period can also set up conditions for VF (Fig. 18–22).

TERMINATION OF DANGEROUS ARRHYTHMIAS

A ventricular arrhythmia is judged to be dangerous (1) when it causes hemodynamic compromise (e.g., low cardiac output with weakness, syncope, or congestive heart failure (CHF); hypotension; or collapse) (Figs. 18–22, 18–24*F,G*), or (2) when it may degenerate into a more electrically unstable and fatal arrhythmia (Fig. 18–23).

Heart rate is the most important determinant of hemodynamic compromise with a tachyarrhythmia (Fig. 18–24). Systolic and diastolic dysfunction are more pronounced in the left ventricle with sustained ventricular tachycardia.[225] For example, slow (120 beat/min), monomorphic VT that is hemodynamically tolerated in a dog with normal myocardial function usually does not demand antiarrhythmic intervention. Treatment of single PVCs is not necessary because the hemodynamic compromise is brief or not significant.

ECG features that imply electrical instability and increase the belief that the arrhythmia should be treated include (1) polymorphic PVCs, (2) a short coupling interval between the PVC and the preceding normal beat (i.e., the premature ventricular complex occurs during the vulnerable period of the T wave [*R on T phenomenon*]), or (3) a short cycle length (i.e., rapid heart rate) for the consecutive ventricular complexes. Rapid, monomorphic or polymorphic VT is more likely to degenerate into VF than is slow (<120 beats/min), monomorphic VT.

ELIMINATION OF CLINICAL SIGNS

Weakness, exercise intolerance, hypotension, and syncope are likely when VT is rapid and sustained (>30 sec).[199] Holter monitoring coupled with a diary of the pet's activities can correlate an arrhythmia with clinical signs when the association is in question.

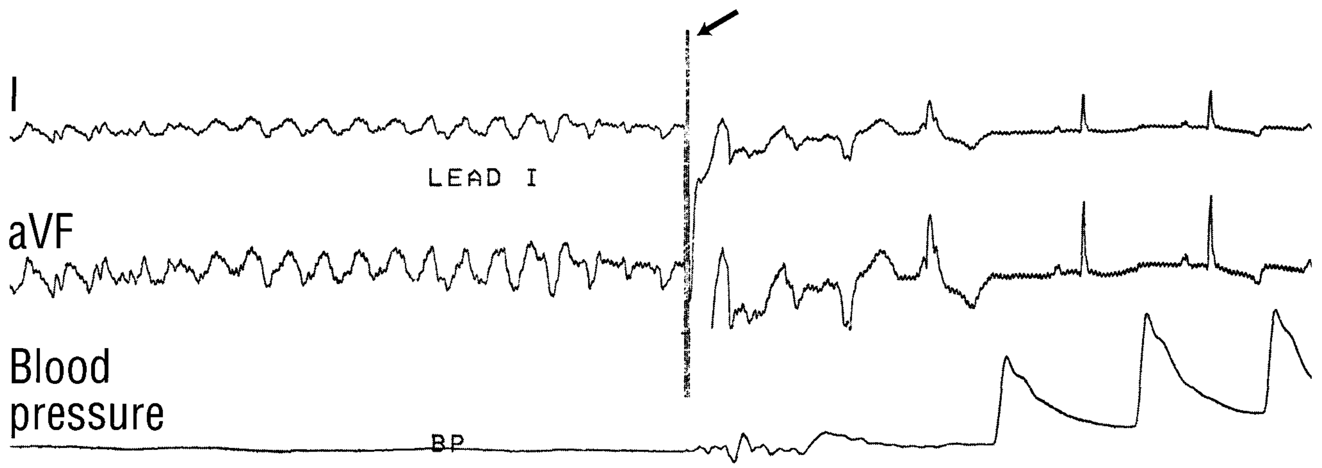


FIGURE 18–22

Simultaneous recording of leads I, aVF, and arterial blood pressure in a German shepherd undergoing implantation of a cardioverter defibrillator device. Testing requires inducing ventricular fibrillation (left half of the tracings) followed by defibrillation (*arrow*). Fibrillation is induced with rapidly repeated electrical stimuli delivered to the left ventricle through a sensing/pacing lead. The ventricular fibrillation is sensed by the implanted device, which issues a shock to defibrillate the heart successfully. Sinus rhythm is then re-established. Notice the absence of an arterial blood pressure during the ventricular fibrillation, and resumption of blood pressure during sinus rhythm.

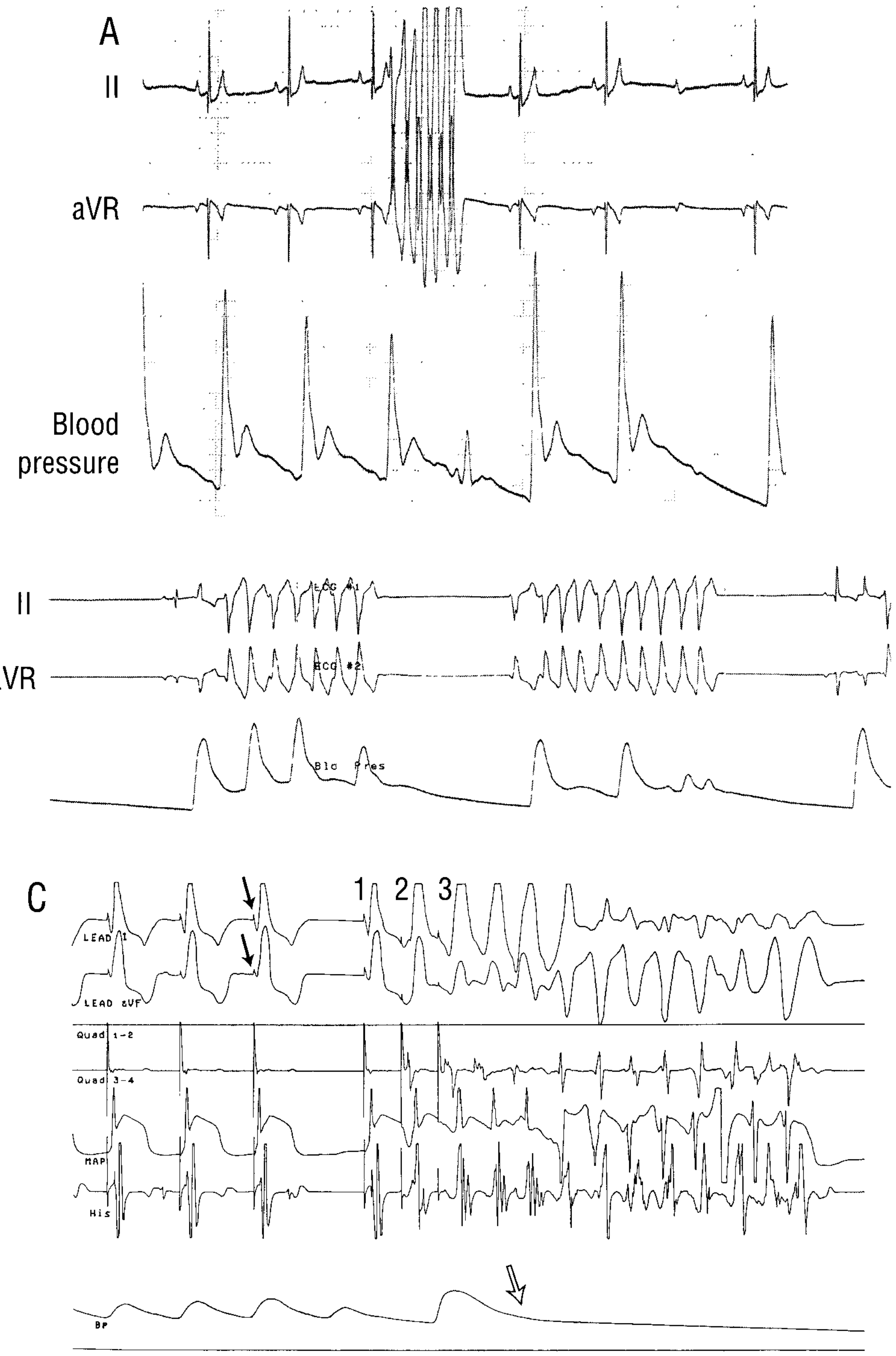


FIGURE 18–23

See legend on opposite page

Natural History and Risk Stratification

When deliberating whether to treat a ventricular arrhythmia, one must also consider the clinical presentation and associated disease. For example, myocardial dysfunction is the major determinant of risk associated with ventricular arrhythmias in humans[226-228]; the extrapolation is most likely true for dogs as well. Even before development of myocardial failure in the cardiomyopathic boxer[229] (and possibly Doberman pinscher), VT and syncope appear to be associated with increased risk of sudden death. German shepherd dogs with rapid VT are at risk of death until 18 months of age, whereas those with only PVCs, or those older than 18 months, are at low risk.[230-233]

APPROACHES AND CRITERIA FOR SUCCESSFUL MANAGEMENT

CONTINUOUS (HOLTER) ECG MONITORING

Standard, brief ECG recordings may be too short to detect VT and may be inaccurate due to the spontaneous hourly variability in arrhythmia frequency.[234-240] Dangerous arrhythmias may be revealed only by 24-hour ECG recordings. Holter monitoring can also help assess antiarrhythmic drug efficacy.[5] To verify a true reduction in the frequency of ventricular arrhythmias requires a minimum of 24 hours of continuous ECG monitoring, rather than just the standard 1- or 2-minute ECG rhythm strip.

Holter monitoring is not without its own limitations. In humans, even with 24 hours of ECG recorded, the day-to-day variability of ventricular arrhythmias is high.[234-240] Variability is greater when the frequency is low (<200 PVC beats/hr) than when the PVC counts are high (>1000 beats/hr). Moreover, when the interval between recordings is increased, the spontaneous variability in arrhythmias varies even more.[237] Therefore, to demonstrate clearly a positive drug effect, (1) re-examination should be made within a short period of time, (2) the percent reduction of arrhythmias should be stringent, (3) long-term follow-up may include examination off drug treatment, and (4) the limitations of monitoring, as they apply, must be factored in. Nevertheless, Holter monitoring provides critical assessment for managing ventricular arrhythmias.[5, 222, 241, 242]

REDUCTION IN ARRHYTHMIA FREQUENCY (REDUCTION OF THE INITIATION OF AN ARRHYTHMIA OR TERMINATION OF A TACHYCARDIA). Based on 48 hours of Holter monitoring in humans, suppression of approximately 90 percent of repetitive ventricular ectopic beats and a 75% reduction in PVCs must be achieved to ascribe an antiarrhythmic effect comfortably.[234] This type of criterion is effective only when ventricular arrhythmias are frequent. Currently, specific recommendations have not been validated for dogs.

REDUCTION IN RATE OF ARRHYTHMIA. In some circumstances, abolishing the VT is not possible, although the antiarrhythmic may effectively decrease the rate of the

FIGURE 18-23

Electrophysiologic recordings that demonstrate the effect of ventricular arrhythmias on systemic (arterial) blood pressure. Ventricular complexes do not generate a blood pressure as effective as complexes that originate from supraventricular tissue and traverse the normal conduction system. The number of ventricular ectopic beats/minute is a determinant of cardiac output, as well as atrial-ventricular synergy (cardiac output = stroke volume × heart rate). Blood pressure represents the product of cardiac output times total peripheral resistance. Thus, the length of time that the heart maintains a rapid ventricular arrhythmia influences clinical signs.

(A) Simultaneous ECG (leads II and aVR) and arterial blood pressure recorded from a dog with rapid, nonsustained ventricular tachycardia. Both the paroxysm of tachycardia and associated fall in blood pressure were brief and thus did not result in observable clinical signs. The postextrasystolic potentiation of the sinus beat that followed the tachycardia is reflected in the increased blood pressure. Paper speed 25 mm/sec.

(B) Simultaneous ECG (lead II and aVR) and arterial blood pressure recorded from a dog with long sinus pauses, ventricular escape complexes, and ventricular tachycardia. The arterial blood pressure is reduced, irregular, and not consistent with each ventricular complex. Such a variation in systemic pressure is also seen with atrial fibrillation. Paper speed 50 mm/sec.

(C) Data generated during ventricular pacing in a German shepherd dog undergoing programmed stimulation (*arrow* is pacing artifact) to determine whether ventricular tachycardia (VT) could be induced. The dog's siblings had died suddenly and unexpectedly from suspected ventricular arrhythmias. These simultaneous recordings included surface ECG leads (I and aVF), intraventricular leads (quad 3–4), monophasic action potential (MAP), and His electrogram (His). Ventricular pacing with a postmature stimulus *(1)* and two premature complexes *(2 and 3)* consistently induced nonsustained, rapid, polymorphic VT and profound depression of arterial blood *(open arrow)*. Such a drop in systemic blood pressure, when sustained more than 8 to 10 seconds, results in clinical signs. Induction of VT in this dog is unusual in German shepherds with inherited VT. Paper speed 100 mm/sec.

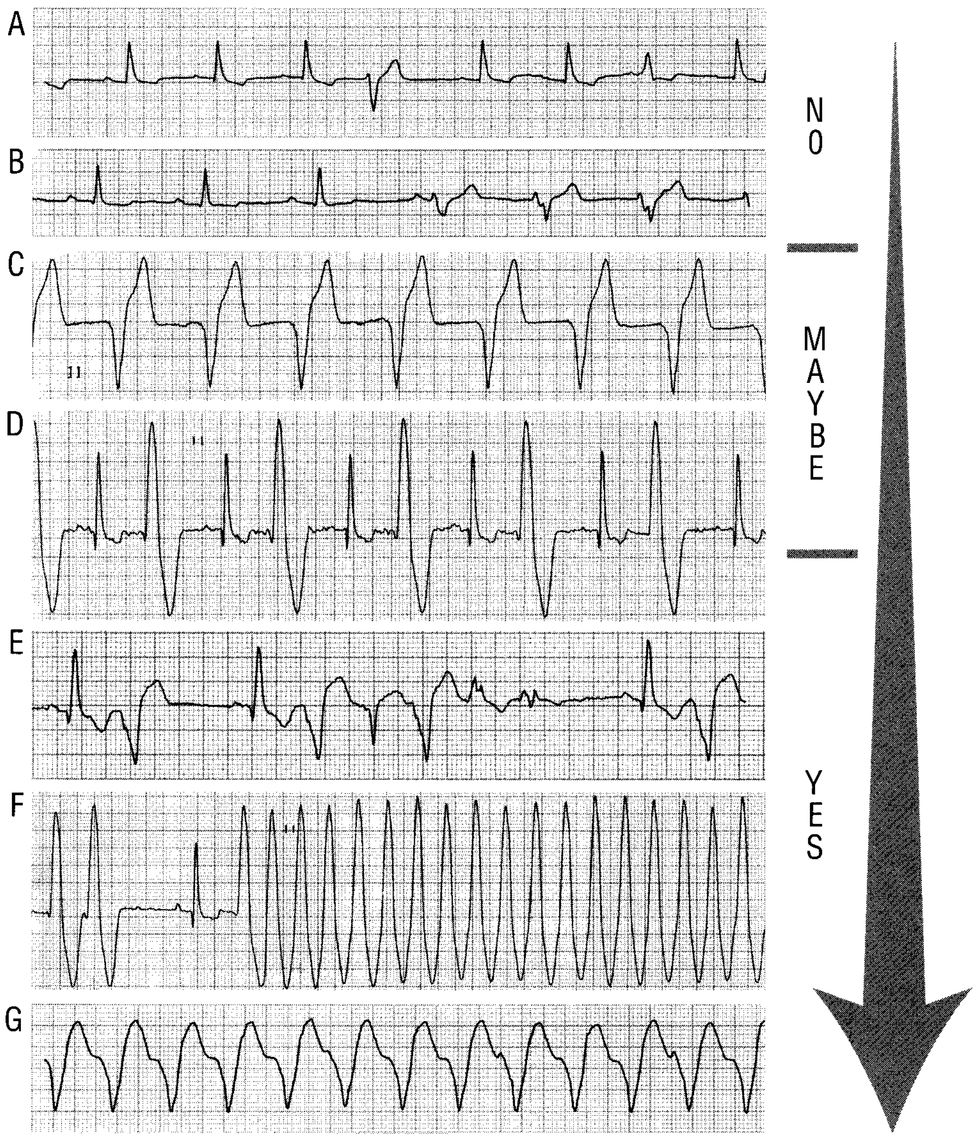


FIGURE 18–24

Composite scheme of ventricular arrhythmias, showing which would be treated. The width of the arrow indicates the increasing need for treatment. The judgment to treat or not on each of these examples is based on the assumption that the short ECG segment is representative of what the dog's ECG is like over a longer period. To be sure of the frequency and severity of the ventricular arrhythmia, a Holter recording for 24 hours would improve the information on which a decision is made to treat. Paper speed 50 mm/sec. (A) Single premature complexes are rarely treated. (B) Monomorphic ventricular triplet at a rate that is similar to the sinus rate. This rhythm would rarely be treated. (C) Monomorphic, slow ventricular tachycardia (120 beats/min) from a dog that was hit by a car. Most dogs with traumatic arrhythmias recover with or without treatment. Therapy should be based on close ECG monitoring and clinical assessment for hemodynamic compromise.

(D) Ventricular bigeminy recorded from a boxer. Although only single premature complexes were recorded, this breed is at high risk for dangerous VT associated with "boxer cardiomyopathy." Therefore, 24-hour Holter recording is recommended to determine whether VT is present; an echocardiogram would be helpful; and close clinical monitoring is important. This dog would probably be treated.

(E) Polymorphic VT recorded from a dog with a splenic mass. Acute antiarrhythmic therapy appears warranted based upon clinical condition and polymorphic QRS complexes. This arrhythmia resolved after splenectomy. (F) Rapid, monomorphic VT with left bundle branch block pattern from a syncopal boxer. Treatment is clearly indicated. (G) Rapid, monomorphic VT in a dog with myocardial failure. AV dissociation is present, and some P waves are visible (notice the 2nd and 5th complexes from the right). Treatment for the heart failure and acute antiarrhythmic therapy are required. Animals with myocardial failure tolerate VT more poorly than those with a functionally normal heart.

tachyarrhythmia. A slower heart rate during VT may be adequate to lessen clinical signs and risk of death.

DRUG EFFECTS ON THE ELECTROCARDIOGRAM

The ECG can often provide evidence of drug efficacy or toxicity (see chapter 17, Table 17–5). Lidocaine, although it blocks sodium channels and causes a delay in ventricular conduction, does not prolong the QRS complex because of rapid unbinding.[243] In contrast, quinidine, procainamide, amiodarone, and sotalol will cause a dose-related prolongation of the QRS complex. Prolongation of the QT interval can also be a marker of drug toxicity in some cases, particularly with drugs that prolong repolarization, such as class Ic and class III drugs (see chapter 17, Tables 17–2, 17–5).[243] Toxicity from class III drugs can cause the development of a U wave and large T waves, which may precede the development of torsades de pointes.[244] The U wave may result from heterogeneity of repolarization or be generated from the M cells of the ventricular myocardium (Fig. 18–25).[245, 246]

PLASMA DRUG CONCENTRATIONS

Although therapeutic drug concentrations do not guarantee effective treatments or arrhythmia control,[247, 248] proper use of this information when available can assist with proper antiarrhythmic dosing.[249] Monitoring plasma drug levels with the goal of identifying a target drug concentration, avoiding low serum levels, or identifying levels in the toxicity range may be helpful in some cases, particularly when digitalis glycosides are used.

Plasma levels of a specific drug do not always account for active metabolites, tissue drug levels, and the fact that the antiarrhythmic effect can span a wide drug concentration. Although plasma concentrations of procainamide can be of value in the dog, lidocaine levels usually are not except in the evaluation of toxicity, because of the wide variation that occurs with clearance, distribution, and binding to α_1-acid glycoprotein. Mexiletine levels are not usually of value because of the overlap between therapeutic and toxic plasma levels.[249, 250] In humans[249] and dogs,[255] the active metabolite of amiodarone, desethylamiodarone, also has antiarrhythmic activity[176, 251] and may be responsible for toxicity; monitoring the parent drug may not provide adequate warning of toxicity. Moreover, correlating dose and plasma levels is complicated because of the tissue uptake and very wide variability in bioavailability.[252–254]

After steady-state equilibrium is established, one must know when to sample patients to obtain trough (minimal) plasma drug concentrations.[249] Only the free, nonprotein-bound drug is available for pharmacologic effect, but most assays measure the total plasma concentration. Thus, if the proportion of a drug bound to plasma proteins is inconsistent, erroneous interpretation can result.

SELECTION OF ANTIARRHYTHMIC DRUGS

Within a drug class (see Table 17–2), lack of efficacy of one agent does not predict that another drug within

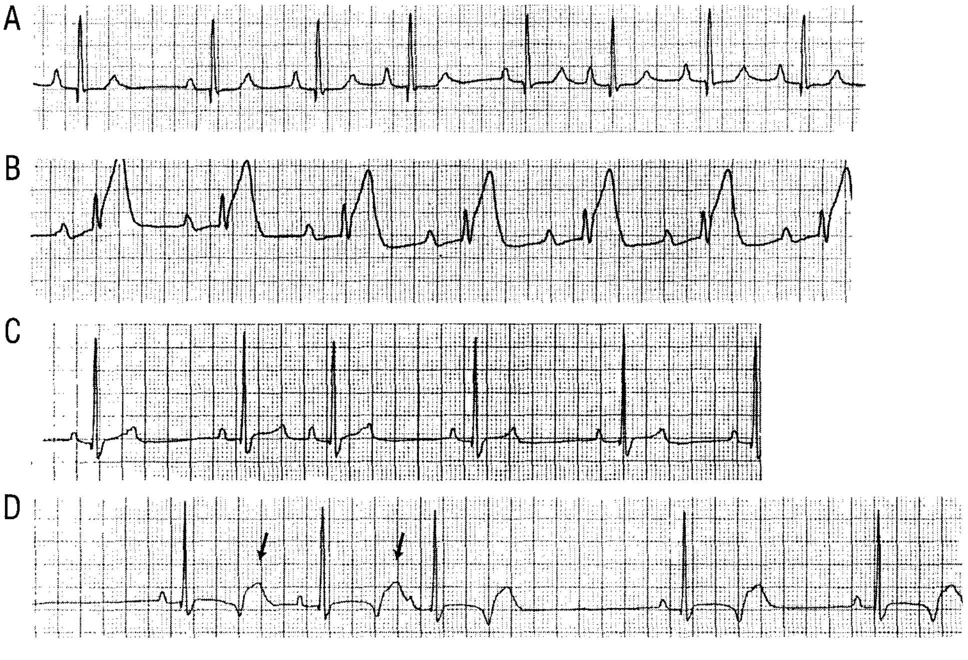


FIGURE 18–25

Class III antiarrhythmics can cause changes in the ECG, such as prolongation of the QT interval, enlargement of the T wave, and development of U waves. (A) ECG of a dog before treatment with a class III antiarrhythmic. (B) Toxicity developed during treatment, and the dog developed large T waves. (C) ECG of another dog before treatment (QT interval = 210 msec). (D) After treatment, this dog developed prolongation of the Q-TU interval (400 msec), large T waves, and U waves *(arrows)*.

that class will be effective or ineffective. Moreover, a treatment response experienced when a drug is administered by a particular route does not indicate a similar response when the agent is given by a different route of administration.[227] Summary comparisons between antiarrhythmic drug classes have been reported in humans.[256–259]

ACUTE (IV, IM) ANTIARRHYTHMIC THERAPY

CONSTANT-RATE DRUG INFUSION

To prepare a constant-rate infusion, several formulas are available to calculate the desired drug dose and infusion rate. Two popular methods are

Body weight (kg) × selected drug dose (μg/kg/min) × 0.36 = total IV dose (in mg) infused over 6 hr

or

Selected drug dose (μg/kg/min) × body weight (kg) = mg of drug added to 250 ml of fluid administered at a drip rate of 15 ml/hr

LIDOCAINE

Clinical Applications

INTRAVENOUS BOLUS ADMINISTRATION. Lidocaine is the most effective drug for acute management and rapid control of life-threatening or unstable ventricular tachyarrhythmias. An IV bolus (2.2 mg/kg) is administered during ECG monitoring. If needed, additional boluses (2.2 mg/kg IV) can be given over approximately 5 minutes, up to a total of 8.8 mg/kg. The half-life is short, and antiarrhythmic effects abate by approximately 10 to 15 minutes, if not sooner. To maintain blood levels, a constant-rate infusion is begun after these initial boluses ("loading doses"). Because lidocaine will take 3 to 6 hours to reach steady state concentration during constant-rate infusion, additional IV boluses (0.25 to 1 mg/kg) may be cautiously repeated as needed.

CONSTANT RATE IV INFUSIONS. Lidocaine may be constantly infused at 25 to 80 μg/kg/min. The foregoing formulas may be used to set up the infusion. Alternatively, starting with a midrange dose of 50 μg/kg/min, withdraw 25 ml from a 500-ml bag of crystalloid fluids (i.e., lactated Ringer's solution with potassium chloride added if renal function is normal), and replace this with 25 ml of 2% (20 mg/ml) lidocaine. This mixture provides a lidocaine concentration of 1000 μg/ml. The IV drip rate may be calculated at the same rate that is used for administering a standard volume of maintenance fluids if CHF is absent (e.g., approximately 70 ml/kg/24 hr). The infusion dose may be increased by delivering a larger volume or by increasing the lidocaine concentration. Infusion pumps facilitate delivering concentrated solutions with minimal fluid volumes. This is desirable when CHF (especially pulmonary edema) is present. When lidocaine is no longer necessary, the infusion may be stopped without tapering. Lidocaine is stored in adipose tissues, and some continues to be released for several hours.[260]

INTRAMUSCULAR ADMINISTRATION. In humans, lidocaine has been administered by the IM route (4 mg/kg) in crisis situations or when IV access is not possible[261, 262]; therapeutic plasma levels occurred within 10 to 15 minutes, with effects lasting about 90 minutes.[262, 263] In dogs, IV administration is the preferred route because of its rapid onset of action; IM administration may be considered as a last resort.

ADVERSE EFFECTS. Lidocaine toxicity can result in CNS signs characterized by twitching, tremors, anxiousness, and seizures. These are usually avoided by careful dose calculation and gradual upward dose titration. If toxicity occurs, lidocaine administration is stopped; IV diazepam is given if neurotoxicity is evident. In the presence of hypokalemia, lidocaine efficacy is severely reduced. A few human studies report depression of blood pressure and cardiac output with high lidocaine doses,[264] with resultant sinus tachycardia, although severe sinus bradycardia has been occasionally noted.[265] In general, lidocaine does not alter hemodynamics except transiently after IV bolus when pre-existing myocardial dysfunction is present. These hemodynamic changes are rarely problematic in dogs with prescribed lidocaine dosages.

Applied Electrophysiologic Actions

HOW LIDOCAINE WORKS. Lidocaine is effective because of its broad antiarrhythmic action against arrhythmias caused by re-entry, normal and abnormal automaticity, and triggered activity (Fig. 18–26).[242] Thus, it may control VT due to any cause. Lidocaine slows conduction in diseased cardiac muscle,[266–268] increases refractoriness while shortening the action potential duration,[269] decreases the dispersion of refractoriness, suppresses phase 4 depolarization,[270] blocks the plateau sodium current,[271, 272] and possibly activates I_{K1}.[271, 272] These characteristics are similar to those of mexiletine (class Ib).

Lidocaine does not control SVTs. This is because its electrophysiologic actions (shortening the action potential and increasing refractoriness) do not affect the atrial myocardium as they affect Purkinje fibers and ventricular myocytes.[260, 263] In atrial myocytes, the action potential duration is already shorter than in the ventricle.[169] The shorter atrial action potential dura-

tion[215] means that the inactivated state is briefer. Therefore, less binding (and less antiarrhythmic effect) can occur in atrial tissue.

USE-DEPENDENCE. An important pharmacokinetic feature of lidocaine is *use-dependence,* the block that develops during the action potential or plateau.[169] A drug has a greater use-dependence when it exhibits a greater antiarrhythmic effect at higher heart rates (Fig. 18–26).[215, 273] Use-dependence is a desirable antiarrhythmic drug quality because rapid tachyarrhythmias are the most dangerous rhythms that require suppression. The onset and offset kinetics of a drug determine its degree of use-dependence.[169] The association and dissociation time constants (the time that it takes for a drug to bind and unbind from the channel receptor) determine these kinetics and account for one of the major differences *within* class I antiarrhythmics (classes Ia, Ib, Ic). During tachycardias, electrical diastole is abbreviated. The time that the cell spends in the inactivated state is greater relative to the resting state; therefore, drugs that bind during inactivation will have enhanced antiarrhythmic effects. Drugs with rapid offset kinetics like lidocaine will build up on the channel receptors during rapid VT but not at slower rates. Therefore, they exhibit more antiarrhythmic effects during VT or on early extrasystolic depolarizations (i.e., complexes with short coupling intervals) because of more drug binding and less unbinding (Fig. 18–26).[215] Late PVCs are less likely to be suppressed by lidocaine, although these are not commonly problematic. Class Ia drugs exhibit use-dependence at slower rates than class Ib drugs, with slower recovery from block, and may be more effective against late PVCs.[274]

Although heart rate is a major determinant for class Ib drug binding, other factors are influential. Lidocaine preferentially binds to more depolarized (less negative potential) cardiac cells because such cellular potential promotes the inactivated state.[275, 276] Partially depolarized cells are usually those that are diseased and generate arrhythmias. Such selectivity of drug binding is advantageous,[169] since more binding occurs with reduced pH and increased extracellular potassium, factors present in diseased myocardium.

PROCAINAMIDE

Clinical Applications

Historically,[277] IV procainamide has been selected as a second-choice drug when lidocaine is ineffective in controlling VT. Procainamide affects normal and abnormal tissues, whereas lidocaine has its maximal effects in depolarized tissues such as those associated with ischemia and infarction.[242, 276, 278] Procainamide is used more safely than quinidine because it has fewer gastrointestinal side effects, has less prolongation of the QT interval, does not interact with digoxin, and causes less hypotension.[277]

INTRAVENOUS ADMINISTRATION. Procainamide (10 to 15 mg/kg) can be administered IV slowly over 1 to 2 minutes to avoid hypotension, although this is uncommon if myocardial function is normal. For continued parenteral administration, procainamide can be given by constant-rate infusion (25 to 50 μg/kg/min). To prepare a 50-μg/kg/min infusion, 5 ml of fluid are removed from 500 ml of lactated Ringer's or other crystalloid solution (with up to 14 mEq of KCl added if serum potassium and renal function are normal); to this, 5 ml of injectable 10% procainamide hydrochloride (100 mg/ml) is added, resulting in a 1000 μg/ml concentration. When infused at a maintenance rate of 70 ml/kg/24 hr (3 ml/kg/hr), a dose of 50 μg/kg/min will be delivered. Alternatively, formulas may be used to make these calculations (see earlier).

INTRAMUSCULAR ADMINISTRATION. Unless the animal is unable to take oral medication, using procainamide IM does not offer benefit over the IV or oral route. The time needed to reach peak plasma levels with IM administration approximates that of oral therapy.[279]

Applied Electrophysiologic Actions

HOW PROCAINAMIDE WORKS. As a class Ia antiarrhythmic agent, procainamide is similar to lidocaine because it depresses membrane responsiveness and slows conduction. However, it differs from lidocaine because it prolongs the effective refractory period while it prolongs the action potential duration. This can result in QRS complex widening, especially at fast heart rates.[280] The latter explains why its antiarrhythmic effects take place in atrial, ventricular, and His-Purkinje fibers. In humans, the active metabolite *N*-acetyl procainamide (see chapter 17) contributes to class III antiarrhythmic, and potentially proarrhythmic, effects; however, this metabolite is not present in dogs. Procainamide decreases the dispersion of refractoriness caused by ischemia (lengthening the action potential duration in the ischemic tissue), suppresses normal and abnormal automaticity, decreases delayed afterdepolarizations, and increases the fibrillation threshold.[279] In some situations, VT may not be eliminated but the heart rate is decreased, thus improving hemodynamic stability.[280]

USE-DEPENDENCE. Class Ia antiarrhythmics such as procainamide exhibit some use-dependence that is similar to that of lidocaine. However, the offset/unbinding of procainamide and other class Ia drugs is intermediate (seconds) between the rapid dissociation of lidocaine (milliseconds) and the slow dissociation of class Ic drugs (10 seconds).[279]

AMIODARONE

Although amiodarone has only recently been used intravenously in humans, its effectiveness in treating refractory VT warrants consideration for selected canine tachyarrhythmias. The electrophysiologic effects of IV amiodarone differ markedly from those associated with chronic oral administration.[281, 282] Experimentally, amiodarone (10 mg/kg/hr) has been effective in dogs that have VT and fibrillation induced by ischemia.[283] In a clinical setting, a bolus of 5 mg/kg can be administered and the dog then evaluated for acute effect in controlling VT.

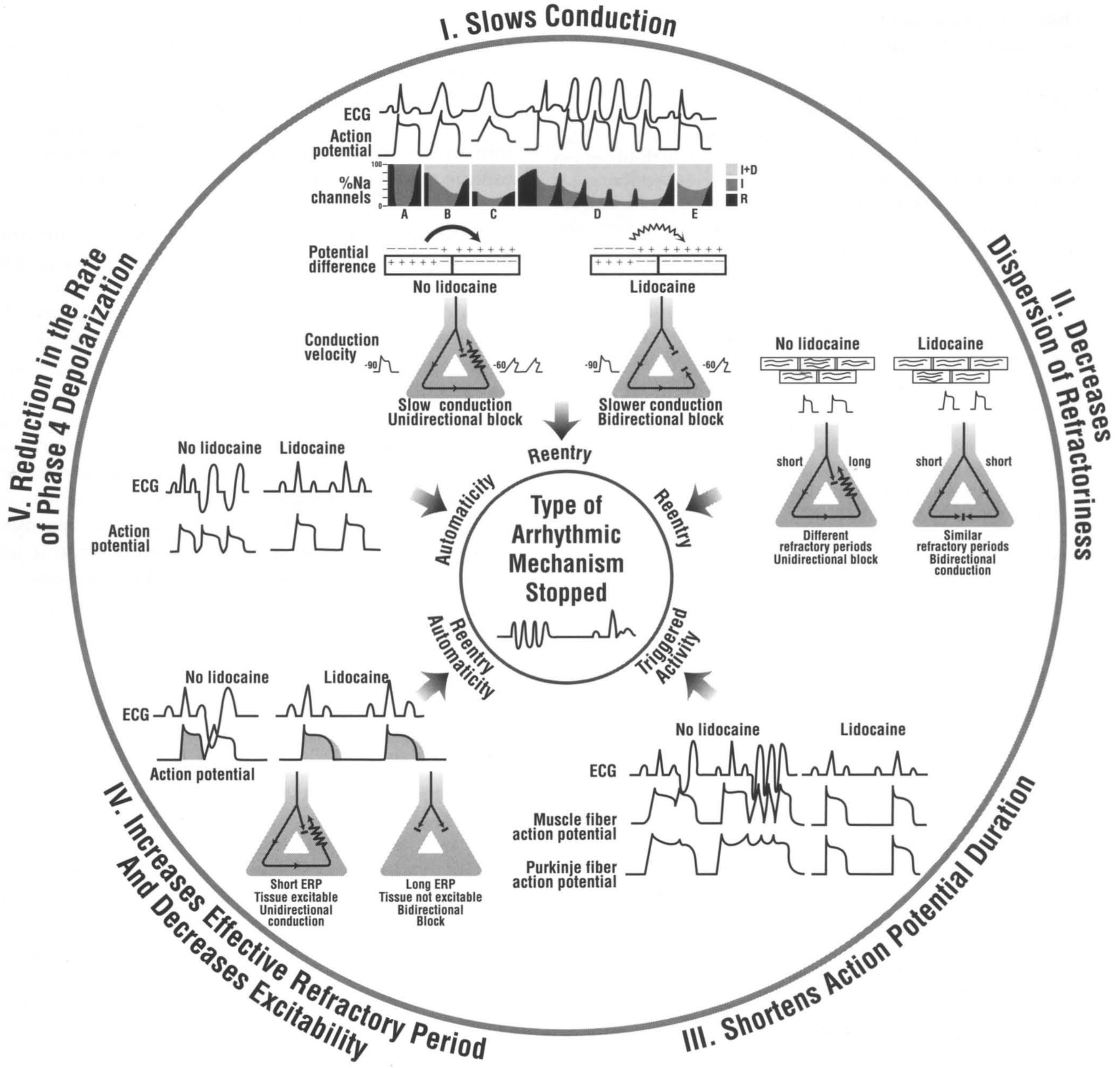


FIGURE 18–26

See legend on opposite page

SOTALOL

The IV formulation of sotalol is available in Europe but not currently in the United States. In humans, the average IV dose is 0.3 mg/kg. Under experimental conditions, doses of greater than 2 mg/kg IV have been administered in the dog.[284] Clinical safety remains to be established.

CHRONIC (ORAL) ANTIARRHYTHMIC THERAPY

PROCAINAMIDE VS. *QUINIDINE*

Clinical Applications

SELECTION AND USE. Procainamide (10 to 20 mg/kg q 6 hrs PO) is usually preferred over quinidine for

chronic maintenance therapy of VT. The sustained-release preparations require less frequent dosing (Procan SR, 10 to 20 mg/kg q 8 hr PO), but obtaining consistent blood levels may be more variable. If arrhythmia control is not obtained after steady-state blood levels are achieved (e.g., approximately 24 hours with procainamide, 36 hours with sustained-release preparations), serum procainamide concentrations may be measured. Samples are drawn 4 to 5 hours after oral procainamide administration or 8 hours after administration of sustained-release preparations. Therapeutic concentrations are uncertain. Procainamide blood levels of 5 to 12 μg/ml may be adequate. In humans, procainamide, and especially quinidine, are now used less frequently because of their proarrhythmic effects. The incidence of proarrhythmias in dogs treated for spontaneous arrhythmias is not known.

MEXILETINE

Clinical Applications

SELECTION AND USE. Some clinicians use mexiletine as a first-line drug for chronic management of canine VTs. Its electrophysiologic properties are similar to those of lidocaine. Therefore, antiarrhythmic effectiveness and untoward effects are comparable. While VT treated successfully with lidocaine is usually effectively treated with mexiletine, the acute effects of lidocaine do not always predict patient response to mexiletine.[285]

Some human studies substantiate the improved antiarrhythmic effect of mexiletine over procainamide and quinidine,[286] although clinical animal trials are lacking. Also, mexiletine may have fewer myocardial depressant effects on left ventricular function,[286] and this may be beneficial in dogs with myocardial failure.

Currently, mexiletine (4 to 8 mg/kg, q 8 hr PO), combined with atenolol (0.5 mg/kg, q 12 to 24 hr PO) is my first choice for chronic oral therapy of dangerous ventricular arrhythmias. Mexiletine costs substantially more than either procainamide or quinidine, but fewer side effects may reduce the overall cost of treatment. Untoward effects (trembling, seizures, depression) are similar to those of lidocaine at toxic doses. Gastrointestinal side effects can usually be limited by giving mexiletine with food. Mexiletine has fewer pro-

FIGURE 18–26

How lidocaine works as an antiarrhythmic. I. *Slows conduction.* Blockade of the sodium channels is the major mechanism for slowing ventricular conduction. Illustrated from top to bottom is an ECG, the corresponding action potentials, the percent (0 to 100%) of available Na^+ channels with the state of the channel (i.e., resting = R, inactivation = I, inactivation with bound drug = I + D). Lidocaine binds and, therefore, blocks the Na^+ channels during inactivation. In A, no lidocaine is present (no I + D shown). During the rest phase, just before the next activation, nearly 100% of the sodium channels are available for opening. The more sodium channels available, the faster the depolarization (steep phase 0 with rapid upstroke, V_{max}). In *B*, lidocaine binds during the inactivation phase to many of the sodium channels. More binding occurs in cells that are partially depolarized, diseased cells *(C)*. Shown here, the resting membrane potential is only −60 mV. Although lidocaine blocks a large fraction of the sodium channels during each plateau (inactivation) phase, the fast diastolic recovery ensures that most channels are unblocked by the next action potential. However, with very early extrasystoles and rapid rates, binding accumulates (use-dependence) *(D)*. Notice how I + D is greater than in *A* or *B*. Beneath this schematic of use-dependence (% Na^+ channels), the effect of the potential difference between depolarized and nondepolarized cells is shown without and with lidocaine. The greater the potential difference, the greater the gradient that propagates the depolarization wave. Lidocaine lessens the potential difference between cells at any point in time during phase 0, decreasing potential driving force and slowing conduction *(irregular arrow)*. This slowed conduction can change an area of unidirectional block into bidirectional block; thereby, stopping re-entry.

II. *Decreases dispersion of refractoriness.* Diseased myocytes vary in the duration of action potential and refractoriness. This promotes re-entrant arrhythmias because some areas will have longer refractory periods, allowing unidirectional block. Lidocaine shortens the action potentials where they may be prolonged, yet increases the effective refractory period in these areas, creating less dispersion of refractoriness. The result is more uniformity of refractoriness and less likelihood of bidirectional block. In some areas, when a premature depolarization wave hits a former area of unidirectional block, conduction proceeds with lidocaine, resulting in the impulse dying without re-entry.

III. *Shortens action potential duration.* Prolonged repolarization from disease or drugs can result in triggered activity. Early afterdepolarizations (EADs) can propagate and result in ventricular arrhythmias. In this illustration, EADs that originate in Purkinje fibers (note small spikes during phase 2 of action potential) propagate to the ventricular muscle. This results in ventricular premature complexes that have reached threshold. The EADs can be inhibited when the action potential is shortened by lidocaine.

IV. *Increases effective refractory period.* Lidocaine can increase the effective refractory period (ERP) even while shortening the action potential duration *(postrepolarization refractoriness)*. This inhibits arrhythmias caused by enhanced abnormal automaticity or re-entry. Automatic stimuli do not result in an action potential because the myocytes remain refractory (gray area representing the ERP extends past the end of the action potential). The longer ERP results in bidirectional block and can arrest re-entrant arrhythmias.

V. *Reduction in the rate of phase 4 diastolic depolarization.* Automatic arrhythmias are lessened because spontaneous depolarizations are inhibited.

arrhythmic effects than the commonly used class Ia drugs.[260] In the United States, mexiletine is currently available for oral use only, although a sustained-release formulation (Perlongets) and IV preparation are available in Europe.

β-*ADRENERGIC BLOCKERS*

Clinical Applications

SELECTION AND USE. The adjunctive use of β-adrenergic blockers to treat VT has been acclaimed in humans based on evidence that they decrease mortality. β-Adrenergic blocker monotherapy may be inadequate for controlling PVCs,[287, 288] although it is particularly effective when PVCs and VT are associated with high circulating catecholamine levels (e.g., during anesthesia with halothane and with exercise).[289] The frequency of PVCs does not reliably predict long-term benefit. In human studies, β-adrenergic blocker monotherapy only modestly affected the incidence of PVCs but decreased mortality.[165, 290] The latter may be due to the antifibrillatory effects of β-adrenergic blockade.[291] Applicability of these studies to clinical veterinary medicine has not been determined. Since β-adrenergic blockers are comparable in their antiarrhythmic effect, selection of a particular agent is determined by other characteristics,[289, 292] including drug kinetics, half-life, and receptor selectivity. Caution must be used if β-adrenergic blockers are given when myocardial failure is present.

Minimal information is available regarding β-adrenergic blocker monotherapy for treatment of VT in dogs. Propranolol (0.5 to 1.5 mg/kg), atenolol (0.5 mg/kg), or metoprolol combined with either procainamide or mexiletine can be effective in some cases. The dose of β-adrenergic blockers must be titrated to achieve the desired therapeutic end points.

ADVERSE EFFECTS

ELECTROPHYSIOLOGIC APPLICATIONS

Antiarrhythmic actions of β-adrenergic blockers may be attributable to direct electrophysiologic mechanisms or to indirect systemic or metabolic effects.[293] If the heart has diseased myocytes that are partially depolarized, these cells, when stimulated by catecholamines, can reach threshold and result in premature complexes that in turn could initiate tachycardia. Furthermore, β-adrenergic blockade will decrease phase 4 spontaneous depolarization, decrease membrane excitability, inhibit adrenergic shortening of refractoriness, and decrease phase 0 upstroke velocity. Very high doses of certain drugs such as propranolol can block the inward sodium "window" current.[293–295]

AMIODARONE AND SOTALOL

Clinical Applications

SELECTION AND USE. Currently, clinical trials evaluating these class III agents are lacking in dogs for treating spontaneous VT. Anecdotal reports give mixed results and may reflect the variation of diseases treated, doses used, and incomplete patient follow-up. Experimentally, sotalol was effective in suppressing canine VT induced by increased sympathetic influences.[284] In humans, sotalol and, especially, amiodarone are becoming more frequently selected as first-line ventricular antiarrhythmic drugs based upon favorable clinical results.[222, 296–298] However, because cardiac disorders (e.g., coronary artery disease) associated with these arrhythmias in humans are rare in dogs, it is unclear whether these drugs would be as effective in canines. It should be emphasized that amiodarone and *dl*-sotalol are not pure class III agents, but both have class II action (amiodarone also possesses class I and class IV activity).

AMIODARONE. When administered orally, amiodarone has a delayed and highly variable onset of action[299] that makes dosing and determination of clinical response difficult. Amiodarone is very lipophilic and protein bound and has a high volume of distribution.[300] Because it can cause severe side effects (see chapter 17, Table 17–6), the goal should always be to use the lowest effective dose. Clinical experience has been limited. A loading dose of 10 mg/kg/24 hr was given to dogs in experimental studies for 7 to 10 days,[283] followed by a maintenance dose of 5 mg/kg daily or three times per week.

SOTALOL. The commercially available preparation is the racemic mixture of *d*- and *l*-sotalol, the dextroisomer having less than 2 percent of the nonselective β-adrenergic blocking activity of the levoisomer.[301] The β-adrenergic blocking activity of *dl*-sotalol is about 30 percent that of propranolol and occurs at lower doses than do the class III actions.[53] Sotalol differs from amiodarone in that sotalol does not bind to plasma proteins; is eliminated through the kidneys; is hydrophilic; lacks active metabolites; and has no effect on digoxin concentrations. Also, long-term administration of sotalol does not alter its kinetics with plasma concentrations proportional to the dose.[302] Canine pharmacokinetic[303] and dose-response studies (Bristol-Myers Squibb, unpublished observations) have been performed and reviewed.[287] The starting dose is 0.5 to 2 mg/kg PO sid to bid.

CLINICAL MONITORING. Studies in humans treated with amiodarone revealed no relationship between dose and efficacy of PVC suppression.[304] The value of

monitoring plasma levels is unclear,[305] although plasma drug concentrations may be of some benefit in determining whether "effective" plasma levels have been attained.[145] Reverse T_3 levels have been used to monitor amiodarone, which blocks the conversion of T_4 to T_3. Elevated levels of reverse T_3 have been associated with adverse effects.[143] Liver and thyroid function, as well as routine biochemistry tests, should be monitored every 6 months. For amiodarone and sotalol the heart rate, Q-T interval, and P-R interval should be monitored (Fig. 18–25).[306–309] Dose-related ECG changes have been well described with sotalol.[308, 309]

ADVERSE EFFECTS. Dose-related side effects with amiodarone include gastrointestinal upsets, pulmonary fibrosis, hyperthyroidism, hypothyroidism, ocular opacities, and hepatic failure.[281] The use of low-dose amiodarone has been touted as a means of achieving antiarrhythmic activity without untoward effects.[185] Proarrhythmias, including torsades de pointes for sotalol, are probably related to excessively high doses.

Amiodarone and sotalol must be used judiciously in the setting of CHF. Amiodarone has a minor but definite negative inotropic effect, which is offset by the lengthening of the action potential duration and associated prolongation of contraction.[198] Consequently, long-term treatment with amiodarone does not worsen or induce CHF because it has few or no net negative inotropic effects.[310] However, concomitant use of digoxin with amiodarone can cause plasma digoxin levels to increase. Sotalol does not affect serum digoxin levels. Moreover, drug interactions with sotalol are infrequent because of its lack of protein binding and biotransformation. However, sotalol can cause a worsening of CHF, lethargy, and bradycardia, which is related to its β-adrenergic blocking activity.[300]

Applied Electrophysiologic Actions

HOW AMIODARONE AND SOTALOL WORK. Electrophysiologic heterogeneity underlies the re-entrant mechanism of many life-threatening ventricular arrhythmias. Amiodarone and sotalol prolong the action potential duration and refractory period without slowing conduction. This class III drug effect makes the action potential pattern more uniform throughout the myocardium (decreases QT dispersion), thereby increasing electrical stability.[309, 311] The β-adrenergic blocking property of each drug also has an antiarrhythmic effect. Although these class III agents are antiarrhythmic, they may exert their greatest effect as antifibrillatory agents that prevent ventricular fibrillation or the VT that precedes VF.[222] The class I and class IV effects of amiodarone also contribute to its antiarrhythmic effects.[269]

ADDITIONAL PROPERTIES. Amiodarone has other physiologic actions that contribute to its effectiveness during poor perfusion, such as its phospholipase inhibition, which prevents the build-up of arrhythmogenic substances during ischemia.[281, 312] Because the molecular structure of amiodarone is similar to that of thyroid hormones, some of its cardiac action is speculated to be due to inhibition in the heart of T_3 nuclear receptors, which then mimics intracellular hypothyroidism.[313]

IMPORTANCE OF REVERSE USE-DEPENDENCE. Drugs with class III action potentially express *reverse use-dependence* (i.e., decreased antiarrhythmic action with faster heart rates). This phenomenon occurs when action potential prolonging (class III) drugs exert their greatest effects at relatively slow heart rates. This is the opposite of the more desirable characteristic, *use-dependence*, defined as increased antiarrhythmic action expressed at faster heart rates (i.e., with tachycardias the antiarrhythmic effect is greater). Reverse use-dependence is an undesirable characteristic because it causes the antiarrhythmic action of a drug to be least effective during tachycardia.[268] Although sotalol exhibits reverse use-dependence, amiodarone does not because it prolongs action potentials to an equivalent degree both at slow and fast rates.[167] This characteristic of amiodarone has been shown in the dog. It may explain the lower incidence of torsades de pointes seen with amiodarone compared with sotalol.[268] Most class III drugs block the rapid component of the delayed rectifier potassium current (I_{kr}), although amiodarone also blocks the inward rectifier current (I_{K1}) and the ATP-sensitive potassium channel($I_{k\text{-}ATP}$).[220] It is the blockade of I_{kr} that causes the maximal prolongation of the action potential and refractoriness to occur at slow rates.[167] Amiodarone does block I_{ks} during the open state, and it is this action that probably maintains its lengthening of action potential duration at fast heart rates, thereby improving its efficacy. Sotalol does not have this effect; thus, reverse use-dependence and torsades de pointes may be related to this difference.

COMBINATION ANTIARRHYTHMIC DRUG THERAPY

Clinical Applications

SELECTION AND USE. Although combining antiarrhythmics can be dangerous, the potential also exists for synergistic effects.[215] In humans[314] and in dogs,[315, 316] combination antiarrhythmic drug therapy can be effective in reducing VT and the induction of VF when monotherapy has failed. Combination therapy may also be better tolerated than maximal dosages of agents used as monotherapy.[317] A common antiarrhythmic drug combination combines a class Ia drug (procainamide or quinidine) with a class Ib drug (lidocaine or mexiletine).[314, 318–320] Class Ia or class Ib drugs are potentially more antiarrhythmic when either is combined with a β-blocker.[317] For example, the effectiveness of mexiletine can be enhanced when given with a β-blocker (atenolol, propranolol, nadolol, or metoprolol). Procainamide or quinidine combined with sotalol has been effective under experimental conditions for treating ventricular arrhythmias.[321] Some agents that are classified as class III drugs actually possess antiar-

rhythmic action characteristic of class II drugs, such as *dl*-sotalol and amiodarone, thereby actually providing combination therapy.

Problems do exist when using antiarrhythmic drug combinations. The effective dose of each drug must be found, and this determination could potentially take more time than using monotherapy. The only statement that can be wisely made with regard to the dosage is to start lower than the dose used for each drug alone. Adverse effects may require the withdrawal of both drugs, although only one drug is really detrimental. Although the reason for drug combinations is synergism, adverse reactions can occur directly from the drugs or because of drug elimination.

Applied Electrophysiologic Actions

Specific electrophysiologic mechanisms underlie the synergistic effects when certain agents (see Table 17–2) are combined. Class Ia drugs such as quinidine prolong the action potential, which allows the sodium channels to remain inactivated for a longer period of time. If a class Ib drug (e.g., mexiletine), which preferentially binds to the inactivated channel, is also given, more time for binding occurs and increased antiarrhythmic effects are possible, even when the dose of each drug is reduced.[317] Catecholamines can actually reverse the antiarrhythmic effects of class I drugs. Therefore, when class II drugs (β-adrenergic blockers) are added to procainamide, quinidine, mexiletine, or lidocaine, this reversal is prevented.[322] Also, the antiarrhythmic effect of prolonging refractoriness by class Ia drugs is increased with β-adrenergic blockade, and this may be due to the effects on potassium currents.[322, 323] When class Ia drugs are used with class III drugs, the effect of reverse use-dependence is decreased.[321] Sympathetic stimulation shortens the action potential duration by increasing the magnitude of I_k currents. Such electrophysiologic effects attenuate the effectiveness of class III drugs.[221, 323] This may in part be why some class III drugs are not as effective, and are potentially dangerous during periods of sympathetic stimulation such as exercise, unless they also possess some class II activity.[269]

REASONS FOR THERAPEUTIC FAILURE

INEFFECTIVE ANTIARRHYTHMIC ACTION

Drugs may be ineffective for many reasons. These include

1. Incorrect arrhythmia diagnosis;
2. Inadequate dosage;
3. Pharmacokinetic complications that reduce serum drug concentrations;
4. Antiarrhythmic drug action that does not override or that potentiates the mechanism underlying the arrhythmia; or
5. Physiologic alterations (i.e., hypokalemia) that hinder the antiarrhythmic action.

If a drug is ineffective, the dose is gradually increased, generally in 25 percent increments. Concurrent disease can alter drug clearance or metabolism (renal or hepatic disease) or change the volume of distribution (CHF) such that frequent dosage adjustments are needed.[263] Drug-arrhythmia mismatch is a difficult problem to detect, although it can be suspected in some situations as when using class III agents in German shepherds with inherited VT (see discussion that follows).

EFFECTS OF HYPOKALEMIA ON ANTIARRHYTHMIC DRUG EFFICACY. Low serum potassium concentrations can result in loss of antiarrhythmic effect of lidocaine.[324] Lidocaine binds during the inactivation state, whereas negligible binding occurs during the resting state. The longer the membrane stays in the resting state (electrical diastole, phase 4), the more time for lidocaine to unbind maximally from the sodium channel. The number of sodium channels available during the resting state depends on the resting membrane potential, such that small changes in the latter can profoundly affect unbinding. With more negative potentials and resulting longer diastolic depolarization, there would be more time for unbinding, and the antiarrhythmic effect would be lessened. During hypokalemia, the driving force for the efflux of potassium from cardiac cells is increased. Therefore, the resting membrane potential is more negative than during normokalemia. The resulting hyperpolarization promotes unbinding, thereby reducing sodium channel blockade by lidocaine, and thus reducing its antiarrhythmic effect. Also, the effect of hypokalemia lowering the resting membrane potential is to increase the upstroke velocity (V_{max}) of phase 0, which enhances conduction velocity. This effect can counteract the decrease in conduction velocity of drugs such as lidocaine. Hyperkalemia can potentiate the slowed conduction. Therefore, with hypokalemia, the effect of lidocaine on the maximal rate of depolarization may be lost entirely. Moreover, hypokalemia makes the heart more sensitive to catecholamines, and the beneficial antiarrhythmic effects are lacking.[325] The action of other drugs such as sotalol also is detrimentally affected by hypokalemia or hypomagnesemia (see discussion that follows).[53, 269]

PROARRHYTHMIA

A *proarrhythmia* is a new arrhythmia or aggravation of pre-existing arrhythmia caused by a drug. Circumstances that make proarrhythmia more likely include CHF, concomitant drug use such as high-dose diuretics, poor systolic function, hypokalemia, or hypomagnesemia. Although different drugs possess different degrees of proarrhythmic tendency, any drug can have such an effect.[274, 326–329] Drugs are considered proarrhythmic when they induce new tachyarrhythmias or bradyarrhythmias. In humans, the incidence of proarrhythmia varies from approximately 5 to 25 percent. Drugs that have been associated with proarrhythmia and are most commonly used in dogs include quinidine, procainamide, and sotalol, but the frequency of this side effect is unknown.

A proarrhythmic effect is established on the basis of increased frequency of ectopic complexes. Interpretation of such an increase must be weighed against the natural variability that occurs in the frequency of arrhythmias. In humans, such a determination is based on 24- to 48-hour Holter recordings, and standards have been established relative to baseline arrhythmia counts. When PVCs are infrequent, spontaneous changes in the frequency of the arrhythmia are greater than when PVCs are frequent. Therefore, a greater increase in the number of PVCs is required for the former to document a proarrhythmic effect. For example, if at baseline 10 to 50 PVCs/hr are present, then a tenfold increase in PVCs/hr must develop during treatment to be considered proarrhythmic. However, if more than 300 PVCs/hr are present at baseline, then a threefold increase is required. For nonsustained VT, the number of events per day must increase tenfold to 20-fold in frequency.[3] Some drugs may decrease the frequency of arrhythmias at rest; however, they may also increase the frequency and severity of an arrhythmia during exercise. Ideally, therefore, for Holter monitoring the ECG should also be recorded during exercise.[330, 331]

Proarrhythmic effects are often associated with higher drug doses, and therefore it is generally recommended that the lowest effective dose be used.[274, 327–329] Although the diastolic rate of drug dissociation is not dependent on drug concentration, onset kinetics is related. This means that class Ia and Ic drugs that have slow unbinding (i.e., offset) kinetics will attain rapid binding (i.e., onset) kinetics with higher doses. As a result, more drug will accumulate and result in toxicity or proarrhythmic effects. However, in some circumstances, low drug doses with low plasma concentrations may actually potentiate an arrhythmia (e.g., quinidine and procainamide).

Arrhythmias that are induced by drugs can be due to potentiation of the underlying mechanism or generation of a new mechanism. In drugs that slow conduction, instead of creating bidirectional block and abolishing the VT, re-entry can be potentiated. Such an action can occur with class Ia and Ic agents. Increases in the dispersion of refractoriness as evidenced from increases in QT dispersion have been documented with class Ia and class III drugs.[332]

TORSADES DE POINTES. This specific ventricular arrhythmia is characterized by a rapid, polymorphic VT that appears to twist around the baseline.[333] Torsades de pointes has been associated with class Ia, class Ic, and class III drugs when Purkinje fibers and midmyocardial cells develop early afterdepolarizations because of coexisting hypokalemia, preexisting QT-interval prolongation, or bradycardia.[248, 268] It may also may be caused by dispersion of refractoriness. Sotalol has a greater incidence of torsades de pointes than amiodarone because it prolongs the Purkinje fibers disproportionately more than myocardial cells.[301] Amiodarone does the converse, and it is this effect that may explain the lower incidence of proarrhythmia with amiodarone.[258] The reverse use-dependence of sotalol also increases its proarrhythmic tendency, and because amiodarone does not exhibit this action but is effective at all stimulation frequencies, again has less of a proarrhythmic effect.[258] This potentially fatal arrhythmia is not necessarily associated with high drug levels but may develop at low dosages and low plasma drug concentrations.

SELECTED CANINE CARDIAC DISEASES WITH ARRHYTHMIAS

BOXER CARDIOMYOPATHY

CLINICAL OVERVIEW. Affected boxer dogs can present with syncope or weakness or CHF or remain asymptomatic for long periods.[229] Dogs experiencing syncope frequently appear normal between episodes. Although some affected dogs have supraventricular arrhythmias, syncope usually results from rapid, sustained VT. Collapse is usually associated with exercise, stress, or excitement, and this is when VT is frequently documented (Fig. 18–21). The VT and PVCs of boxer cardiomyopathy usually have a distinctive left bundle branch morphology similar to that observed in humans with right ventricular outflow tract VT. Some boxers may have only PVCs documented for years before VT is encountered. The value of treating boxer dogs that have only PVCs is unknown, and the natural history of this disease has not been described. Boxers with VT have a high risk for sudden death, and treatment is recommended.

THERAPY. Because the sympathetic nervous system influences initiation of VT in these dogs, drugs that block sympathetic tone may be of greater benefit than drugs devoid of this action. Mexiletine (4 to 8 mg/kg q 8 hr PO) combined with atenolol (12.5 to 25 mg q 12 to 24 hr PO) has decreased the frequency of VT and abolished syncope in some affected boxers. Based on more limited experience, amiodarone or sotalol has been found to have similar favorable results. However, each of these treatment regimens is currently more expensive than procainamide (10 to 20 mg/kg q 8 hr PO) combined with propranolol (0.5 to 1.0 mg/kg q 8 hr PO),[229] which in some dogs results in an adequate response. Treatment is for the life of the dog. Some dogs will go years with medically controlled arrhythmias but eventually develop myocardial failure and congestion. Arrhythmias may be exacerbated when CHF is present, requiring additional therapies (see chapters 12 and 27).

DILATED CARDIOMYOPATHY IN DOBERMAN PINSCHERS

CLINICAL OVERVIEW. Doberman pinschers with myocardial dysfunction can die suddenly.[334, 335] The cause

of death usually is suspected of being VT that degenerates into VF, although bradycardias may be the cause in some cases. VT in the Doberman does not have a distinctive morphologic characteristic. Monomorphic or polymorphic VT is common.

THERAPY. Successful antiarrhythmic management can be difficult because of concurrent heart failure and systolic dysfunction. Therefore, use of antiarrhythmic drugs (i.e., quinidine, *d*-sotalol) that have potential negative inotropic effects may result in decompensation. Consideration of potential drug interactions (e.g., digoxin and quinidine) is important. Advice in this circumstance is to control the CHF and then treat with an antiarrhythmic as needed, with close follow-up to assess response (see chapters 12 and 17).

SUDDEN DEATH IN GERMAN SHEPHERDS

CLINICAL OVERVIEW. Inherited ventricular arrhythmias and a proclivity for sudden death have been identified in German shepherd dogs.[13, 230–233, 336–340] Affected animals do not have syncope. Sudden death, which most often occurs during presumed sleep or when the dog is at rest, is the only observed physical indication of the disorder.[13, 230] Dogs usually die between 4 and 18 months of age, and the postmortem examination does not reveal the cause of death.[230] Physical examination is usually normal unless an arrhythmia is detected. Since arrhythmias are dependent on behavior and heart rate,[13] a routine ECG will reveal arrhythmias in only the most severely affected animals. Diagnosis usually requires Holter monitoring,[8, 13, 233] although even this may not identify all affected dogs because the arrhythmias are also age dependent.[233] Standard ECG measurements, chest radiographs, biochemical profiles, and echocardiography are normal.

Affected dogs have a spectrum of ventricular arrhythmias. Dogs at risk for sudden death have VT that is rapid, polymorphic, nonsustained, and preceded by a pause.[230, 233] Therefore, the frequency and severity of arrhythmias are greater during periods of pronounced sinus arrhythmia. Slowing of the heart rate by direct vagal stimulation or through stimulation of baroreceptors with α_1-adrenergic agonists enhances the VT.[340] Some dogs have slower (200 to 250 beats/min), monomorphic, sustained VT whereas others have only single PVCs.[230, 233]

Dogs usually do not have arrhythmias before 12 weeks of age.[233] Thereafter, arrhythmias can be detected, and the frequency of ventricular arrhythmias increases such that the greatest number occur between 24 and 30 weeks of age. Subsequently, a portion of dogs remains fairly static in the frequency and severity of their arrhythmias, whereas others develop progressively more severe arrhythmias and die suddenly.[230, 233] Other dogs as they age have a reduction in the frequency of the arrhythmias, even to the point of never having arrhythmias again after 18 months of age.[230, 233]

Arrhythmias are most frequent during rest or sleep. Multiple factors determine the frequency of the arrhythmias during certain behavioral states.[13] Excitement and ambulating presumably are accompanied by high sympathetic tone and vagal withdrawal, which would account for fewer sinus pauses during these behaviors. This is in contrast to the slower heart rate and frequent sinus pauses that occur during sleep.

MECHANISMS. German shepherd dogs with VT have abnormal sympathetic innervation to the heart and early afterdepolarizations.[337, 339] Scintigraphy using ^{123}I-metaiodobenzylguanidine (MIBG) has revealed abnormal distribution of sympathetic innervation in affected dogs.[337] Lack of innervation also was confirmed by immunocytochemical staining of tyrosine hydroxylase in sections of heart muscle. Histologic examination has revealed markedly reduced numbers of sympathetic nerve terminals in areas of the heart that failed to take up MIBG. Purkinje fibers located in the areas of the heart lacking innervation develop triggered activity secondary to early afterdepolarizations, and this is one mechanism for the initiation of the VT.[339] Delayed afterdepolarizations may be involved as well. Preliminary studies reveal that affected dogs have excessive β-adrenergic receptors when compared with age-matched control dogs. Such a situation would predispose to arrhythmogenic effects of the sympathetic system; perhaps this would be enhanced during concomitant increased parasympathetic activation.

THERAPY. Most affected dogs do not require treatment because (1) arrhythmias are not associated with clinical signs, (2) the incidence of arrhythmias in most affected dogs is low, and (3) after the animals are 18 months old, the probability of death is low.[233] However, dogs with frequent episodes of rapid VT (>10 runs/24 hr) have a high probability of death, with more than half of these dogs dying suddenly. Unfortunately, a single oral medication has not been identified that consistently prevents sudden death. Intravenous lidocaine is very effective in acutely abolishing the arrhythmias; however, long-term treatment with a variety of antiarrhythmics has yielded mixed results. Some antiarrhythmics that prolong the action potential duration, such as sotalol, may actually provoke the arrhythmias. Pacing to keep the heart rate above 130 beats/min does reduce the frequency of VT but may not effectively prevent sudden death in severely affected dogs. No consistently effective oral drug has been identified to treat affected dogs with VT. Initial therapy with mexiletine is generally recommended, combined with a follow-up by continuous (Holter) ECG recordings to document its effectiveness. Also, once a severely affected dog reaches the age of 2 years, then withdrawal of the drug is possible. If an affected dog requires anesthesia, the VT is usually controlled (unless the dog is severely affected) as long as parasympatholytic agents are given.

COMMON CLINICAL CONDITIONS ASSOCIATED WITH VENTRICULAR ARRHYTHMIAS

CONGESTIVE HEART FAILURE

Ventricular arrhythmias are common in dogs with CHF due to dilated cardiomyopathy (chapter 27) and chronic, acquired valve disease (endocardiosis) (chapter 25). In humans, nonsustained VT is an independent marker of increased mortality due to sudden death in states of CHF.[341] Arrhythmias may occur with heart failure because of myocardial hypertrophy, fibrosis, local ischemia, electrolyte imbalances, catecholamines, or myocardial stretch.[228, 342] Myocardial hypertrophy can result in slowed conduction and heterogeneous increases in refractoriness, both of which contribute to re-entry. Similarly, fibrosis provides the substrate for re-entry because conduction velocity is slowed by decreasing the electrical coupling between cells. Hypertrophy also prolongs the action potential duration, making triggered activity more likely.[228] With heart failure, prolonged action potential duration and abnormal repolarization are believed due in part to a reduction in the inward rectifier K^+ current I_{K1} and I_{to}.[237] These changes are not necessarily uniform in the failing heart, which leads to increased dispersion of refractoriness that predisposes to re-entrant arrhythmias.

Hypokalemia and hypomagnesemia have been implicated as causes for arrhythmias in CHF. Increased catecholamines are arrhythmogenic as they increase intracellular calcium, causing delayed afterdepolarizations, and increase heterogeneity of recovery times, causing re-entry. Stretching of myocytes increases abnormal automaticity and triggered activity.[343, 344]

GASTRIC TORSION/VOLVULUS, HEAD TRAUMA, SPLENIC MASSES, AND CARDIAC TUMORS

Dogs with these conditions can develop ventricular arrhythmias. Electrolyte imbalance, poor coronary perfusion, catecholamines, and circulatory shock contribute to the arrhythmogenesis of gastric torsion/volvulus. The reason for ventricular arrhythmias in dogs with cranial trauma is hypothesized to be due to excessive myocardial catecholamine levels, resulting in small myocardial infarctions. Because of the link between the CNS and the heart in the generation of ventricular arrhythmias, the term "brain-heart syndrome" has been used. The mechanism for the arrhythmias associated with splenic masses is unknown, although microscopic metastasis of tumor to ventricular myocardium has been detected in some dogs with splenic hemangiosarcoma (Fox PR, personal communication, 1998). Cardiac tumors can cause regional conduction delay and enhance the substrate for re-entry.

THERAPY. In these conditions, treatment involves managing the underlying diseases. Pharmacologic management and stabilization of the heart failure state (chapter 12) can decrease the frequency of arrhythmias.[228] Antiarrhythmic therapy has been associated with greater mortality in humans with CHF,[345] and even assessment of antiarrhythmic drug efficacy may be difficult owing to high day-to-day variability in arrhythmia frequency.[346, 347] In contrast, dogs with gastric torsion and brain-heart syndromes may require short-term IV antiarrhythmic drug therapy with lidocaine when severe VT is encountered. With brain-heart syndrome, the use of β-adrenergic blockers has been advocated by some clinicians, although clinical data are lacking. Most ventricular arrhythmias associated with splenic masses are not severe. However, if dangerous VT is present, pre- and intraoperative IV lidocaine administration is advocated. After splenectomy, antiarrhythmic therapy is usually not required. When cardiac tumors are associated with ventricular arrhythmias, pharmacologic therapy is frequently unrewarding, and life-threatening VT can occur in advanced cases.

BRADYARRHYTHMIAS

CLASSIFICATION OF BRADYCARDIAS

The most common bradyarrhythmias that demand treatment include marked sinus bradycardia, sinus node dysfunction (sick sinus syndrome), high-grade 2° AV block, 3° (complete) AV block, and persistent atrial standstill.

SINUS BRADYCARDIA

DEFINITION, ECG FEATURES. The parameters of sinus bradycardia (SB) will vary depending on the breed and personality of the dog. As a general guideline, it is present when (1) heart rate is less than 60 beats/min in an awake yet calm large-breed or athletic dog, or (2) heart rate is less than 90 beats/min in a nervous small-breed dog. The circumstances under which the heart rate is determined will influence the rate and must be factored into the deliberation. As discussed under the section on Holter monitoring, very slow sinus rates, exaggerated sinus arrhythmia, and long sinus pauses can be found during sleep in normal dogs.[12, 13] The heart rate is likely to be slower when determined by auscultation in a quiet room than from the routine ECG recording.

Exercise intolerance, weakness, syncope, or CHF

may result if the heart rate is excessively slow for a substantial period of time. The latter occurs when the SB is related to the sick sinus syndrome. Most dogs with SB have no clinical signs, or the signs are so insidious that they go unnoticed. Alternatively, SB may be detected in dogs that have other, more serious medical problems. While concern in these cases may be focused on an apparently slow heart rate, diminution of blood flow to other organs and related clinical significance is often difficult to verify.

Clinical signs should be correlated and matched with relevant ECG findings. This may require the use of 24-hour Holter monitoring, although even with this diagnostic test, discovery of an association may still be difficult if the signs are intermittent. An inappropriate sinus node response to exercise can be examined if the dog can be exercised and an ECG recorded immediately after. Ideally, such a test is performed with the dog wearing a Holter monitor.

It may be difficult to ascertain whether SB is the result of vagotonia or pathologic causes. Some appreciation of the influence of the parasympathetic system can be obtained by challenge with a vagolytic drug such as atropine. Although SB caused by pathology will frequently respond somewhat, it will be less than that caused by physiologically mediated SB. Unfortunately, it is not clear what constitutes a full response to a parasympatholytic agent in dogs. Moreover, this will vary with the size and breed. Recommendations have included a 50 to 100 percent increase in heart rate (dependent on the initial heart rate), or achieving a heart rate above 150 beats/min. Atropine may be administered IV or IM (0.02 to 0.04 mg/kg). When low doses of atropine are used or the drug is injected rapidly IV, a paradoxic increase in vagus-induced bradycardia frequently results.[348] Also, a differential vagolytic effect may occur between the SA node and the AV node such that the sinus node discharge frequency increases before the conduction through the AV node accommodates to the increase. This results in varying degrees of AV block (Fig. 18–27).

MECHANISMS. Sinus bradycardia may be physiologic, pharmacologic, or pathologic. Differentiation is important in formulating treatment decisions. Physiologic SB is a normal response to increased parasympathetic tone and decreased sympathetic tone as occurs during sleep. However, the SB may be a physiologic response to a pathologic condition that has resulted in excessive vagotonia. Such conditions include gastrointestinal (e.g., intestinal obstruction), central nervous system (e.g., elevated intracranial pressure), genitourinary (e.g., urethral obstruction), respiratory (e.g., lower airway obstruction) or pharyngeal (e.g., brachiocephalic syndrome) disorders.[348] Hypothermia and electrolyte imbalances such as hyperkalemia can cause SB.[349] Drugs such as β-adrenergic blockers, calcium channel blockers, narcotics, digoxin, IV contrast agents, or anticholinesterases can cause excessive SB. Pathology of the sinus node may be the result of infiltrative neoplastic or inflammatory disease. Alternatively, SB may exist as a primary problem and, therefore, part of the clinical syndrome classified as a sinus node disorder or sick sinus syndrome (SSS).

Sinus bradycardia may be the result of decreased impulse initiation, slowed intranodal conduction, or exit block. In physiologic SB, acetylcholine decreases the automatic rate of diastolic depolarization that decreases impulse initiation. This occurs because the potassium channel I_{KACH} is activated, hyperpolarizing the membrane and bringing the sinus node P (pacing) cells farther from threshold.[24-26] Moreover, increased vagal tone decreases the slope of phase 4 depolarization.[350] Conduction in the sinus node is slow (2 to 5 cm/sec),[350] such that disease (i.e., fibrosis) that disrupts the intercellular connections could cause enough impairment to hinder conduction with the result of sinoatrial block.

Exit block and sinus arrest are diagnosed when the distance between P waves is some multiple of the basic sinus rate. Exit block means that a sinus impulse was initiated but it was unable to exit from the sinus node region to elicit depolarization of the surrounding atrial tissue. Diagnosis of exit block in the dog is very difficult because the underlying sinus arrhythmia prevents any consistent measurements of intervals between complexes. Similarly, the diagnosis of a sinus arrest (loss of impulse formation) is complicated by the varied P-P intervals that are characteristic of marked sinus arrhythmia. Furthermore, block in the sinus node may be Möbitz type I (Wenckebach) or type II.[351] With the former, progressive P-P interval shortening that occurs before the dropped P wave is difficult to discern due to the sinus arrhythmia. The traditional rule that specified requiring twice the previous P-P interval to establish a diagnosis of sinus arrest or exit block is oversimplified.

SINUS NODE DYSFUNCTION (SICK SINUS SYNDROME)

DEFINITION, ECG FEATURES. Disorders of the sinus node are known as sinus node dysfunction or sick sinus syndrome (SSS). They result from inadequate impulse formation or conduction that, although influenced by autonomic tone, is pathologic. This disease primarily affects the sinus node, but abnormalities of the AV node and subsidiary pacemakers can coexist in both humans[352] and dogs.[349] The coexistence of abnormal subsidiary pacemakers means that very long pauses (excessively slow escape rate or rhythm) develop when the sinus node is not controlling the ventricular rate. When the sinus node fails to propagate, the next secondary pacemaker to depolarize the heart should originate from the junctional tissues. Although this occurs in dogs with SSS, escape beats frequently originate from Purkinje fibers or ventricular myocytes.

Several ECG abnormalities can be grouped as SSS. These include nonphysiologic SB, chronotropic incompetence (inappropriate SB for the circumstances), sinus pauses, or SB with periods of SVT that is of nonsinus origin[353] (see previous discussion under SVT) (Fig. 18–28). Excessively slow ventricular response rates have been recognized in some dogs with atrial fibrillation (see Fig. 18–13), but whether or not this is also associated with sinus node disease has not been documented.

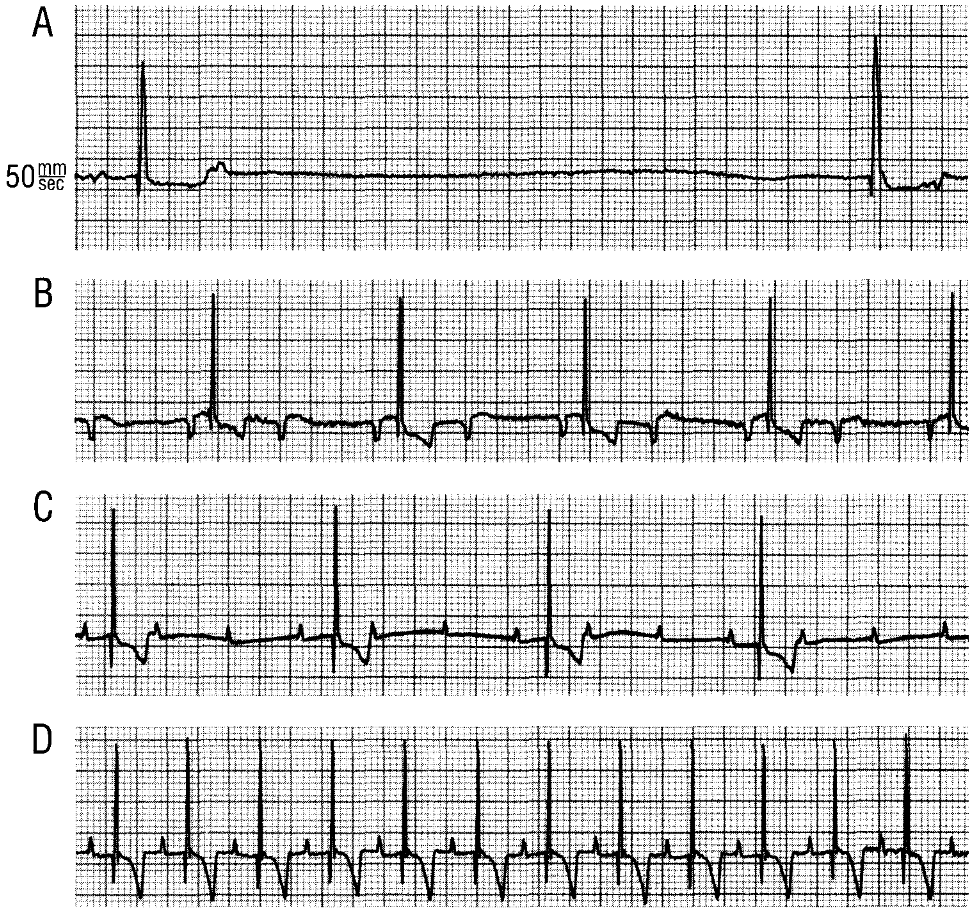


FIGURE 18–27

Lead II recordings from a dog with disease of the SA node. They demonstrate that AV nodal conduction can lag behind the increased sinus rate induced by the atropine. Because this dog had first-degree heart block at a rate of only 120 beats/min, its AV node was abnormal in addition to the sinus node. (A) 50 mm/sec; (B–D) 25 mm/sec; 1 mV = 1 cm. (A) An escape beat (far right), probably originating from junctional tissue, breaks a 5-second pause in the rhythm. (B) Two minutes after atropine administration (0.04 mg/kg IM), negative P waves are evident (indicating that the origin was low in the atrium and most likely near the coronary sinus) with 2:1 AV nodal block. (C) Ten minutes after atropine administration, the P waves became positive with 2:1 and 3:1 AV block. (D) Eighteen minutes after atropine, AV nodal conduction was 1:1 with first-degree block. Heart rate was 120 beats/min.

CLINICAL PRESENTATION. As previously discussed (see earlier comments on SVTs), SSS is most commonly identified in miniature schnauzers, West Highland white terriers, and dachshunds.[349] Sick sinus syndrome is almost exclusively detected in middle-aged, female miniature schnauzers. Although a tachycardia can be a part of this syndrome, many dogs are presented with clinical signs due to SB or sinus pauses. Syncope is a common complaint and is associated with pauses of at least 8 seconds in duration. Some dogs will not have overt clinical signs, but bradycardia will be detected during routine physical examination. The prevalence of this subclinical (semi-) SSS is unknown. Such dogs should be followed for the development of clinical signs related to severe SB or sinus pauses. If the bradycardia is marked—even if clinical signs have not been observed—clinical improvement is usually noted when these dogs are paced. It is important to note that many dogs with SSS also have mitral valve incompetence from endocardiosis, which must be considered within the overall diagnostic and treatment strategy.

DIAGNOSIS. A common feature of SSS is prominent sinus pauses that may occasionally be captured on a lead II ECG rhythm strip. In many cases, extended Holter monitoring coupled with a diary of clinical signs can be pivotal in diagnosing SSS in a dog with syncope (Fig. 18–28). When clinical signs are infrequent, more extensive monitoring, including 24- to 48-hour Holter recordings, is usually required.

An autonomic (extrinsic) component may contribute to the pathophysiology of SSS in which a dog exhibits an excessive response to enhanced vagal tone. As described under SB earlier, recording an ECG after atropine administration can help determine whether intrinsic sinus node disease exists. That is, physiologically mediated SB due to vagotonia will be highly responsive to the vagolytic effects of atropine, whereas with sinoatrial node pathology, the response will usually be blunted. Although the sinus pauses that occur in some dogs can be eliminated with atropine, such responses do not mean that the SSS is benign, and in most cases, pacemaker implantation is still usually required. Vagal maneuvers cause marked SB or the induction of sinus pauses greater than 3 seconds in duration in dogs with SSS.

Another indication of true sinus node disease is a low intrinsic heart rate.[85] To determine the intrinsic rate, both the sympathetic and parasympathetic systems are blocked. Propranolol is administered IV (0.01 mg/kg) over 1 minute, and atropine is administered IV (0.04 mg/kg) over 2 minutes.[85, 348] The spontaneous

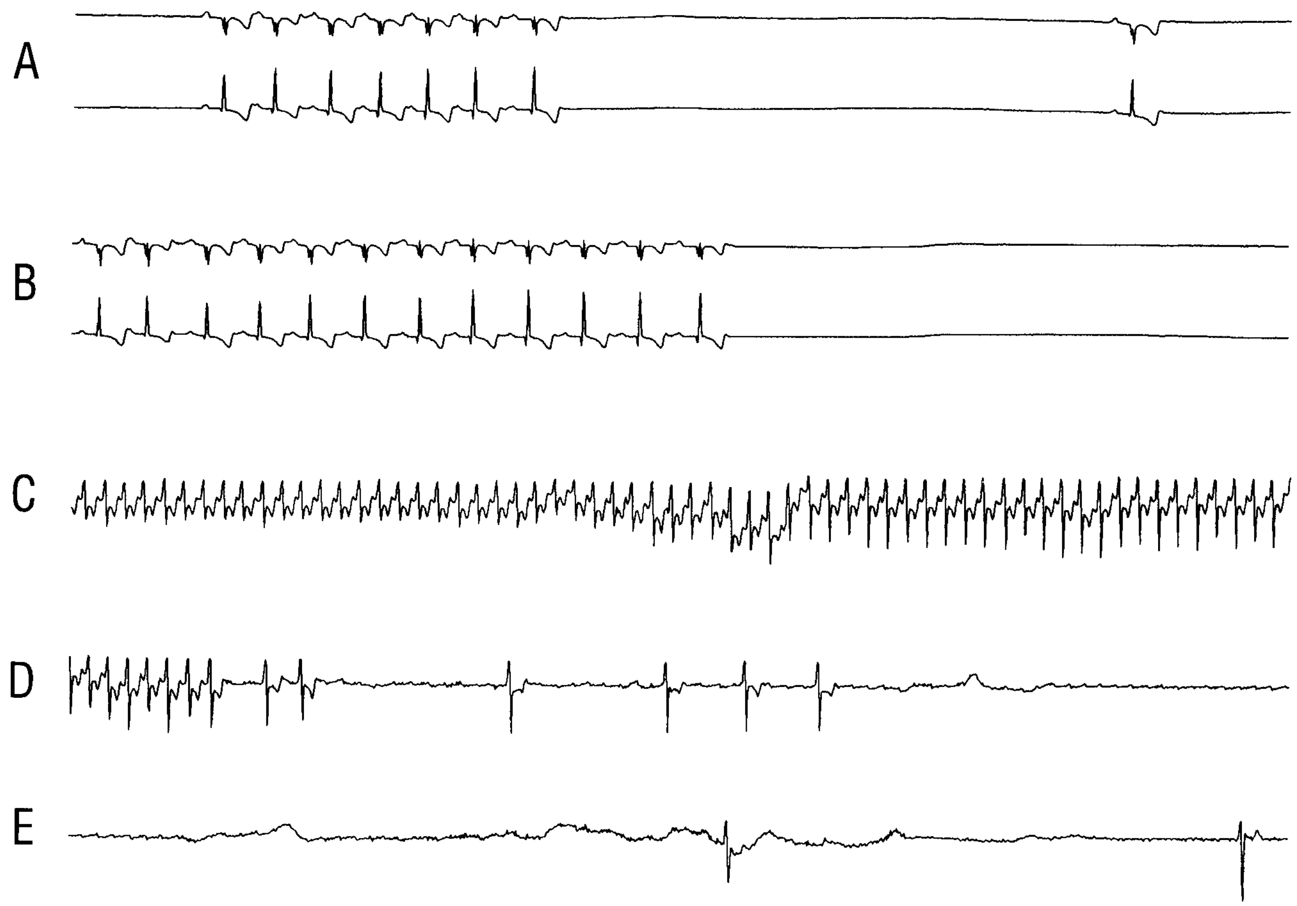


FIGURE 18–28

Holter ECG recordings from two dogs with abnormal sinus node function. (A and B) Two simultaneous leads recorded from a 4-year-old boxer with syncope. (A, B) Sinus pauses exceeding 10 seconds are present. Runs of supraventricular (SVT) and ventricular tachycardia were later recorded. (C to E) Single lead Holter recording from a West Highland white terrier with sick sinus syndrome. Periods of SVT (C) were followed by long intervals of sinus arrest (D and E) that were associated with syncope. In this dog the SVT P waves were negative. However, because a P-R interval was present and since the arrhythmia persisted even with high-grade AV block, both typical and atypical AV nodal re-entrant tachycardia were ruled out. A low atrial origination of the SVT would explain the negative T waves. A pacemaker controlled the bradycardia, but the SVT was resistant to antiarrhythmic therapies.

inherent rate of the sinus node reported in the normal young dog is approximately 100 beats/min.[85] In humans,[354, 355] and probably in dogs, the intrinsic heart rate is influenced by age.

The sinus nodal discharge rate is normally dominant over latent pacemaker cells. This is because the SA node depolarizes more rapidly, caused by a phenomenon called *overdrive suppression*. In the latter, prolonged suppression of normal SA nodal pacemaker cells is proportional to the rate and duration of a more rapidly discharging pacemaker. The diseased sinus node is more susceptible to overdrive suppression than normal, or to the effects of more negative surrounding latent pacemaker cells that control the heart rate.[356]

MECHANISMS. Fibrosis of the sinus node is one possible mechanism for the SSS. However, the location of the fibrosis may be of more importance than the amount,[357, 358] because fibrosis develops with aging but does not always result in SSS.[359] The previous discussions relating the nonphysiologic reasons for SB apply to the mechanism of SSS.

OVERDRIVE SUPPRESSION. This results from driving a pacemaker cell faster than its intrinsic, spontaneous rate and is mediated by increased activation of the Na/K ATPase exchange pump. This generates a net outward (hyperpolarizing) Na^+ current that suppresses spontaneous impulse formation in subsidiary pacemaker cells. When the dominant pacemaker activity ceases, the subsidiary pacemaker activity is suppressed, creating a period of quiescence until the intracellular Na^+ current diminishes enough to allow subsidiary cells to reach threshold and initiate the next impulse. Usually the pacemaker that depolarizes the fastest is the sinus node, but when it fails, subsidiary pacemakers are no longer suppressed and they can reach threshold. With SSS, the sinus

node can itself be suppressed, either by spontaneous SVT (tachycardia/bradycardia) or with electrophysiologic testing.[360–362]

ATRIOVENTRICULAR NODAL BLOCK

DEFINITION, ECG FEATURES. Atrioventricular nodal block may be incomplete (1° and 2°) or complete (3°) (see chapter 6). Clinical signs are associated with either high-grade 2° or with 3° AV blocks. First-degree AV block or low-grade 2° AV block can occur in elderly dogs (especially the cocker spaniel), young puppies, or brachycephalic breeds without causing clinical signs.

CLINICAL PRESENTATION. The severity of the clinical signs depends on (1) the severity of heart block, (2) the rate of the intervening escape rhythm, and (3) the state of underlying myocardial function or concomitant cardiovascular disease. Clinically affected dogs are most frequently older, although rarely puppies are identified with congenital heart block. Although some dogs with advanced AV block may be asymptomatic, most have exercise intolerance, weakness, syncope, or CHF. Jugular distention or pulses may be identified. The loudness of the first heart sound will fluctuate with the varied timing of ventricular and atrial systole. As myocardial function is usually normal and the slow heart rate facilitates maximal ventricular diastolic filling, one can usually palpate very strong-to-bounding femoral arterial pulses and demonstrate a high fractional shortening by echocardiography. Radiography and echocardiography frequently reveal cardiomegaly that reverts toward normal (unless cardiomyopathy or endocardiosis is present) after successful pacemaker therapy.

MECHANISM. Fibrosis or occasionally inflammation of the AV node is usually associated with advanced heart block (chapter 36). The AV node normally conducts slowly and has *decremental conduction*—that is, the depolarization wavefront diminishes progressively as it travels in through the AV node.[363] This feature, combined with its structural characteristics of small, sparsely distributed fibers interconnected in a complex network, makes AV nodal impulses susceptible to block when fibrosis or inflammation is present.

ATRIAL STANDSTILL

DEFINITION, ECG FEATURES. Atrial standstill occurs when the atria fail to depolarize from a sinus-initiated impulse. P waves are not present on the ECG, and junctional or ventricular escape beats are responsible for ventricular depolarizations. The English springer spaniel is a breed at risk for this arrhythmia. These dogs may concurrently have temporal muscle atrophy. Biatrial enlargement and congestive heart failure may occur.

MECHANISMS. Although P waves are consistently absent on the ECG, the sinus node usually continues to fire but is ineffective in depolarizing the atria and penetrating the AV node. In English springer spaniels, the atrial myocardium is replaced by fibrosis. If intracardiac recordings reveal atrial electrograms, some atrial muscle exists that is capable of depolarizing, although it is not able to propagate an impulse to the AV node.

THERAPY

Permanent pacemaker implantation is the ideal treatment (see chapter 20) for SSS (which includes pathologic SB); high-grade 2° AV block; 3° (complete) AV block; and persistent atrial standstill. Pharmacologic therapy is usually of limited value. However, parasympatholytic (e.g., atropine, glycopyrrolate) or sympathomimetic (e.g., isoproterenol, dobutamine) agents are sometimes administered in hopes of increasing the ventricular response rate and reducing signs associated with severe bradyarrhythmias. When possible, specific therapies directed to correct underlying diseases associated with vagotonia are given. In dogs and humans,[364] treatment of SSS with theophylline has occasionally resulted in clinical improvement. Anecdotal reports of other therapies have included terbutaline. The beneficial result of these therapies is usually limited by tachyphylaxis.

Although parenteral administration of parasympatholytic drugs such as atropine may reduce the SB and sinus pauses in some dogs with SSS, long-term control using oral therapies is disappointing. During pacemaker implantation if temporary pacing is not available, atropine is sometimes administered in an effort to increase the heart rate. However, atropine can also exacerbate the tachycardia/bradycardia syndrome in some dogs. Complete (3°) AV block is rarely responsive to parasympatholytic or sympathomimetic drugs. Ideal treatment involves temporary pacing and expedient permanent pacemaker implantation (chapter 20).

REFERENCES

1. Sheffield LT, Berson A, Bragg-Remschel D, et al. Recommendations for standards of instrumentation and practice in the use of ambulatory electrocardiography. Circulation 71:626A, 1985
2. Knoebel SB, Williams SV, Achord JL, et al. Clinical competence in ambulatory electrocardiography: a statement for physicians from the AHA/ACC/ACP task force on clinical privileges in cardiology. Circulation 88:337, 1993
3. Morganroth J. Evaluation of antiarrhythmic therapy using Holter monitoring. Am J Cardiol 62:18H, 1988
4. ESVEM Investigators. The ESVEM trial. Electrophysiologic study versus electrocardiographic monitoring for selection of antiarrhythmic therapy of ventricular tachycardia. Circulation 70:1354, 1989
5. ESVEM Investigators–Mason JW. A comparison of elec-

trophysiologic testing with Holter monitoring to predict antiarrhythmic drug efficacy for ventricular tachyarrhythmias. N Engl J Med 329:445, 1993
6. Reiter MJ, Mann DE, Reiffel JE, et al. Significance and incidence of concordance of the drug efficacy predilections by Holter monitoring and electrophysiologic study in the ESVEM trial. Circulation 91:1988, 1995
7. Reiter MJ, Karagounis LA, Mann DE, et al. Reproducibility of drug efficacy predictions by Holter monitoring in the electrophysiologic study versus electrocardiographic monitoring (ESVEM) trial. Am J Cardiol 79:315, 1997
8. Moïse NS, De Francesco T. Twenty-four hour ambulatory electrocardiography. *In* Kirk RW (ed): Current Veterinary Therapy XII. Philadelphia, WB Saunders, 1995, p 792
9. Ulloa HM, Houston BJ, Altrogge DM. Arrhythmia prevalence during ambulatory electrocardiographic monitoring of beagles. Am J Vet Res 56:274, 1995
10. Kostis JB, McCrone K, Moreyra AE, et al. Premature ventricular complexes in the absence of identifiable heart disease. Circulation 63:1351, 1981
11. Patterson DF, Detweiler DK, Huben K, et al. Spontaneous abnormal cardiac arrhythmias and conduction disturbances in the dog. Am J Vet Res 22:355, 1961
12. Kirby DA, Verrier RL. Differential effects of sleep stage on coronary hemodynamic function. Am J Physiol 256:H1378, 1989
13. Moïse NS, Dugger DA, Brittain D, et al. Relationship of ventricular tachycardia to sleep/wakefulness in a model of sudden cardiac death. Pediatr Res 40:344, 1996
14. Andries E, Brugada P, Brugada J, et al. Section VI: Specific arrhythmias. A practical approach to the diagnosis of a tachycardia with a wide QRS complex. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 1002
15. Stewart RB, Bardy GH, Greene HL. Wide complex tachycardia: misdiagnosis and outcome after emergency therapy. Ann Intern Med 104:766, 1986
16. Tchou P, Young P, Mahmud R, et al. Useful clinical criteria for the diagnosis of ventricular tachycardia. Am J Med 84:53, 1988
17. Kastor JA, Horowitz LN, Harken AH, et al. Clinical electrophysiology of ventricular tachycardia. N Engl J Med 304:1004, 1981
18. Waxman MB, Cameron DA, Wald RW, et al. The use of autonomic maneuvers for diagnosis and treatment of cardiac arrhythmias. *In* Wagner GS, Waugh RA, Ramo BW (eds): Cardiac Arrhythmias. New York, Churchill Livingstone, 1983, p 57
19. Boineau JP, Schuessler RB, Cain ME, et al. Activation mapping during normal atrial rhythms and atrial flutter. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1990, p 537
20. Strauss H, Saroff A, Bigger JR, et al. Premature atrial stimulation as a key to the understanding of sinoatrial conduction in man. Circulation 47:86, 1973
21. Dhingra R, Wyndham C, Amat-Y-Leon F, et al. Sinus nodal responses to atrial extrastimuli in patients without apparent sinus node disease. Am J Cardiol 36:445, 1975
22. Arnold RW, Dyer JA, Gould AB Jr, et al. Sensitivity to vasovagal maneuvers in normal children and adults. Mayo Clin Proc 66:797, 1991
23. Waxman MB, Wald RW, Sharma AD, et al. Vagal techniques for termination of paroxysmal supraventricular tachycardia. Am J Cardiol 46:655, 1980
24. Loffelholz K, Pappano AJ. The parasympathetic neuroeffector junction of the heart. Pharmacol Rev 37:1, 1985
25. Salata JJ, Jalife J. "Fade" of hyperpolarizing responses to vagal stimulation at the sinoatrial and atrioventricular nodes of the rabbit heart. Circ Res 56:718, 1985
26. DiFrancesco D, Tromba C. Acetylcholine inhibits activation of the cardiac hyperpolarizing-activated current I_f. Pflügers Arch 410:139, 1987
27. Waxman MB, Cameron DA, Wald RW. Interactions between the autonomic system and supraventricular tachycardia in humans. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1995, p 699
28. Kienzle MG. Section III: Pathologic changes associated with arrhythmia. Autonomic nervous system: parasympathetic influence in cardiac electrophysiology. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 168
29. Lesh MD, Kalman JM. To fumble flutter or tackle "tach"? Toward updated classifiers for atrial tachyarrhythmias. J Cardiovasc Electrophysiol 7:460, 1996
30. Fogoros RN. The electrophysiology study in the evaluation of supraventricular tachyarrhythmias. *In* Practical Cardiac Diagnosis: Electrophysiologic Testing. Boston, Blackwell Scientific Publications, 1991, p 102
31. Sano T, Sawanobori T, Adanlya H. Mechanism of rhythm determination among pace-maker cells of the mammalian sinus node. Am J Physiol 235:H379, 1978
32. Kirchhoff CJHJ, Bonke FIM, Allessie MA. Sinus node reentry: fact or fiction. *In* Brugada P, Wellens HJJ (eds): Cardiac Arrhythmias: Where to Go from Here? Mount Kisco, NY, Futura, 1987, p 53
33. Wellens HJJ. Role of sinus reentry in the genesis of sustained cardiac arrhythmias. *In* Bonke FIM (ed): The Sinus Node. Structure, Function, and Clinical Relevance. The Hague, The Netherlands, Martinus Nijhoff, 1978, p 422
34. Naccarelli GV, Shih HT, Jalal S. Sinus node reentry and atrial tachycardias. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1995, p 607
35. Wellens H, Brugada P. Mechanisms of supraventricular tachycardia. Am J Cardiol 62:10D, 1988
36. Garson A, Gillette P. Electrophysiologic studies of supraventricular tachycardia in children. Clinical electrophysiologic correlations. Am Heart J 102:233, 1981
37. Kunze K, Kuck K, Schluter M, et al. Effect of encainide and flecainide on chronic ectopic atrial tachycardia. J Am Coll Cardiol 7:1121, 1986
38. Creamer J, Nathan A, Camm A. Successful treatment of atrial tachycardias with flecainide acetate. Br Heart J 53:164, 1985
39. Hluchy J, Milovsky V, Uhliarikova H. Triggered activity as the proposed mechanism of left atrial tachycardia induced by premature ventricular beats. Int J Cardiol 34:342, 1992
40. Wyndham C, Arnsdorf M, Levitsky J, et al. Successful surgical excision of focal paroxysmal atrial tachycardia. Circulation 62:1365, 1980
41. Lerman BB, Belardinelli L, West A, et al. Adenosine-sensitive ventricular tachycardia evidence suggesting cyclic AMP-mediated triggered activity. Circulation 74:270, 1986
42. January CT, Riddle JM. Early afterdepolarizations: mechanisms of induction and block. A role for L-type Ca^{++}-current. Circ Res 64:977, 1989

43. Kass RS, Tsien RW, Weingart R. Ionic basis of transient inward current induced by strophanthidin in cardiac Purkinje fibers. J Physiol (Lond) 281:209, 1978
44. Goldberger JJ, Kadish AH. Section VI: Specific arrhythmias. Atrial premature depolarizations, junctional premature depolarizations, multifocal atrial tachycardia, and atrial tachycardia. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 768
45. Josephson ME. Supraventricular tachycardias. *In* Josephson ME (ed): Clinical Cardiac Electrophysiology. Techniques and Interpretations. Philadelphia, Lea & Febiger, 1993, p 181
46. Kopelman H, Horowitz L. Efficacy and toxicity of amiodarone for the treatment of supraventricular tachyarrhythmias. Prog Cardiovasc Dis 31:355, 1989
47. Camm AJ, Obel OA. Epidemiology and mechanism of atrial fibrillation and atrial flutter. Am J Cardiol 78:3, 1996
48. Yamashita T, Inoue H, Nozaki A, et al. Role of anatomic architecture in sustained atrial reentry and double potentials. Am Heart J 124:938, 1992
49. Feld GK, Shahandeh-Rad F. Mechanism of double potentials recorded during sustained atrial flutter in the canine right atrial crush-injury model. Circulation 86:628, 1992
50. Shimizu A, Igarashi M, Rudy Y, et al. Insights into atrial flutter from experimental models. Abstract. PACE 14:627, 1991
51. Marriott HJL. Pearls and Pitfalls in Electrocardiography: Pithy, Practical Pointers. Philadelphia, Lea & Febiger, 1990, p 8
52. Pritchett ELC, McCarthy EA, Wilkinson WE. Propafenone treatment of symptomatic paroxysmal supraventricular arrhythmias: a randomized, placebo-controlled, crossover trial in patients tolerating oral therapy. Ann Intern Med 114:539, 1991
53. Anderson JL. Sotalol, bretylium, and other class 3 antiarrhythmics. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 450
54. Bonagura JB, Ware WA. Atrial fibrillation in the dog: clinical findings in 81 cases. J Am Anim Hosp Assoc 22:111, 1986
55. Bonagura JB. Atrial arrhythmias. *In* Kirk RW (ed): Current Veterinary Therapy X. Philadelphia, WB Saunders, 1989, p 271
56. Bohn FK, Patterson DF, Pyle RL. Atrial fibrillation in dogs. Br Vet J 127:485, 1971
57. Patterson DF, Detweiler DK, Hubben K, et al. Spontaneous abnormal cardiac arrhythmias and conduction disturbances in the dog. Am J Vet Res 22:355, 1961
58. Waldo AL. Mechanisms of atrial fibrillation, atrial flutter and ectopic atrial tachycardia—a brief review. Circulation 75(suppl III):37, 1987
59. Waldo AL. Clinical evaluation and therapy of patients with atrial fibrillation and flutter. Cardiol Clin 8:479, 1990
60. Waldo AL. Atrial fibrillation following open heart surgery. *In* Olsson SB, Allessie MA, Campbell RWF (eds): Atrial Fibrillation—Mechanisms and Therapeutic Strategies. Armonk, NY, Futura Publishing, 1994, p 211
61. Moore EN, Spear JF. Natural occurrence and experimental initiation of atrial fibrillation in different animal species. *In* Gulbertus HE, Olsson SB, Schlepper M (eds): Atrial Fibrillation. Molndal, Sweden, Lindgren and Soner, 1982, p 33
62. Coumel P, Thomas O, Leenhardt A. Drug therapy for prevention of atrial fibrillation. Am J Cardiol 77:3A, 1996
63. Zipes DP. Atrial fibrillation: from cell to bedside. J Cardiovasc Electrophysiol 8:927, 1997
64. Coumel P, Attuel P, Lavallée, et al. Syndrome d'arythmie auriculaire d'origine vagale. Arch Mal Coeur 71:645, 1978
65. Coumel P. Neural aspects of paroxysmal atrial fibrillation. *In* Falk RH, Podrid JP (eds): Atrial fibrillation mechanisms and management. New York, Raven Press, 1992, p 109
66. Satoh T, Zipes DP. Unequal atrial stretch in dogs increases dispersion of refractoriness conducive to developing atrial fibrillation. J Cardiovasc Electrophysiol 7:833, 1996
67. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. Am Heart J 58:59, 1959
68. Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. Arch Int Pharmacodyn Ther 140:183, 1962
69. Moe GK. Evidence for reentry as a mechanism for cardiac arrhythmias. Rev Physiol Biochem Pharmacol 72:56, 1975
70. Allessie MA, Rensma PL, Brugada J, et al. Pathophysiology of atrial fibrillation. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1990, p 548
71. Allessie MA, Konings K, Kirchhof CJHJ, et al. Electrophysiologic mechanisms of perpetuation of atrial fibrillation. Am J Cardiol 77:10A, 1996
72. Allessie MA, Lammers WJEP, Bonke FIM, et al. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. *In* Zipes DP, Jalife J (eds): Cardiac Arrhythmias. New York, Grune & Stratton, 1985, p 265
73. Rensma PL, Allessie MA, Lammers WJEP, et al. The length of the excitation wave as an index for the susceptibility of reentrant atrial arrhythmias. Circ Res 62:395, 1988
74. Rensma PL, Allessie MA, Lammers WJEP, et al. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ Res 62:395, 1990
75. Smeets JLRM, Allessie MA, Lammers WJEP, et al. The wavelength of the cardiac impulse and reentrant arrhythmias in isolated rabbit atrium. Circ Res 58:96, 1986
76. Draper MH, Mya-Tu M. A comparison of the conduction velocity in cardiac tissues of various mammals. Q J Exp Physiol 44:91, 1959
77. Sommer JR, Johnson EA. Comparative ultrastructure of cardiac cell membrane specializations. A review. Am J Cardiol 25:184, 1970
78. Meijler FL. Atrioventricular conduction versus heart size from mouse to whale. J Am Coll Cardiol 5:363, 1985
79. Wang J, Bourne GW, Wang Z, et al. Comparative mechanism of antiarrhythmic drug action in experimental atrial fibrillation. Importance of use-dependent effects on refractoriness. Circulation 88:1030, 1993
80. Hewlett AW, Wilson FN. Coarse auricular fibrillation in man. Arch Intern Med 15:786, 1915
81. Nelson RM, Jenson CB, Davis RW. Differential atrial arrhythmias in cardiac surgical patients. J Thorac Cardiovasc Surg 58:581, 1969
82. Wells JL, Karp RB, Kouchoukos NT, et al. Characterization of atrial fibrillation in man: studies following open heart surgery. PACE 1:426, 1978
83. Wijffels MCEF, Kirchhof CJHJ, Boersman LVA, et al.

Atrial fibrillation begets atrial fibrillation. *In* Olsson SB, Allessie MA, Campbell RWF (eds): Atrial Fibrillation: Mechanisms and Therapeutic Strategies. Armonk, NY, Futura Publishing, 1994, p 195
84. Wijffels MCEF, Kirchhof CJHJ, Dorland R, et al. Atrial fibrillation begets atrial fibrillation: a study in awake, chronically instrumented goats. Circulation 92:1954, 1995
85. Elvan A, Wylie K, Zipes DP. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs. Circulation 94:2953, 1996
86. Goette A, Honeycutt C, Langberg JJ. Electrical remodeling in atrial fibrillation. Circulation 94:2968, 1996
87. Tieleman RG, De Langen CDJ, Van Gelder IC, et al. Verapamil reduces tachycardia-induced electrical remodeling of the atria. Circulation 95:1945, 1997
88. Borders M, Ausma J, Thone F, et al. Structural changes of atrial myocardium after chronic atrial fibrillation in the goat. Circulation 98(suppl I):1593, 1996
89. Meijler FL, Jalife J, Beaumont J, et al. AV nodal function during atrial fibrillation: the role of electronic modulation of propagation. J Cardiovasc Electrophysiol 7:843, 1996
90. Akhtar M, Damato AN, Ruskin JN, et al. Antegrade and retrograde conduction characteristics in three patterns of paroxysmal atrioventricular junctional reentrant tachycardia. Am Heart J 95:22, 1978
91. Akhtar M, Jazayeri MR, Sra J, et al. Atrioventricular nodal reentry: clinical, electrophysiological, and therapeutic considerations. Circulation 88:282, 1993
92. Fogel RI, Prystowsky EN. Section VI: Specific arrhythmias. Atrioventricular nodal reentry. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 828
93. Chung EK. Principles of Cardiac Arrhythmias. Baltimore, Williams & Wilkins, 1989, p 495
94. Atkins CE, Kanter R, Wright K, et al. Orthodromic reciprocating tachycardia and heart failure in a dog with a concealed posteroseptal accessory pathway. J Vet Intern Med 9:43, 1995
95. Hill BL, Tilley LP. Ventricular preexcitation in seven dogs and nine cats. J Am Vet Med Assoc 187:1026, 1985
96. Tilley LP. Ventricular preexcitation and the Wolff-Parkinson-White syndrome. *In* Essentials of Canine and Feline Electrocardiography, 3rd ed. Philadelphia, Lea & Febiger, 1993, p 179
97. Smith WM, Gallagher JJ, Kerr CR, et al. The electrophysiologic basis and management of symptomatic recurrent tachycardia in patients with Ebstein's anomaly of the tricuspid valve. Am J Cardiol 49:1223, 1981
98. Podrid PJ, Fuchs T, Candinas R. Role of sympathetic nervous system in the genesis of ventricular arrhythmia. Circulation 82(suppl I):I-103, 1990
99. Coumel P, Leenhardt A. Mental activity, adrenergic modulation, and cardiac arrhythmias in patients with heart disease. Circulation 83(suppl II):II-58, 1991
100. Switzer DF, Waldo AL, Henthorn RW. Hemodynamic effects of tachycardia. A. Supraventricular tachycardia. *In* Saksena S, Goldschlager N (eds): Electrical Therapy for Cardiac Arrhythmias. Philadelphia, WB Saunders, 1990, p 467
101. Packer DL, Bardy GH, Worley S, et al. Tachycardia-induced cardiomyopathy: a reversible form of left ventricular dysfunction. Am J Cardiol 57:563, 1986
102. Kaab S, Nuss HB, Chiamvimonvat N, et al. Ionic mechanism of action potential prolongation in ventricular myocytes from dogs with pacing-induced heart failure. Circ Res 78:262, 1996
103. Williams RE, Cass DA, Kawagoe Y, et al. Endomyocardial gene expression during the development of pacing-induced heart failure in the dog. Circ Res 75:615, 1994
104. Graettinger JS, Carleton RA, Muenster JJ. Circulatory consequences of changes in cardiac rhythm produced in patients by transthoracic direct-current shock. J Clin Invest 43:2290, 1964
105. Killip T, Baer RA. Hemodynamic effects after reversion from atrial fibrillation to sinus rhythm by precordial shock. J Clin Invest 45:658, 1966
106. Sopher SM, Camm AJ. Atrial fibrillation: maintenance of sinus rhythm versus rate control. Am J Cardiol 77:24A, 1996
107. White CW, Kerber RE, Weiss HR, et al. The effects of atrial fibrillation on atrial pressure-volume and flow relationships. Circ Res 51:205, 1982
108. Wellens HJJ, Brugada P, Smeets JLRM. Antiarrhythmic drugs for supraventricular tachycardia. Am J Cardiol 62:69L, 1988
109. Haines DE, DiMarco JP. Current therapy for supraventricular tachycardia. Curr Probl Cardiol 11:1, 1992
110. Singh BN, Nademanee K, Baky S. Calcium antagonists: clinical uses in treating arrhythmias. Drugs 25:125, 1983
111. Huycke EC, Sung RJ, Dias VC, et al. Intravenous diltiazem for termination of re-entrant supraventricular tachycardia; a placebo-controlled, randomized, double-blind, multicenter study. J Am Coll Cardiol 13:538, 1989
112. Betriu A, Chaitman BR, Bourassa MG, et al. Beneficial effect of intravenous diltiazem in the acute management of supraventricular tachyarrhythmias. Circulation 67:88, 1983
113. Hung JS, Yeh SJ, Liu FC, et al. Usefulness of intravenous diltiazem in predicting subsequent electrophysiologic and clinical responses to oral diltiazem. Am J Cardiol 54:1259, 1984
114. Yeh SH, Liu FC, Chan YY, et al. Termination of paroxysmal supraventricular tachycardia with a single oral dose of diltiazem and propranolol. Circulation 71:104, 1985
115. Winniford MD, Fulton MD, Hillis DL, et al. Long-term therapy of paroxysmal supraventricular tachycardia: a randomized, double-blind comparison of digoxin, propranolol and verapamil. Am J Cardiol 54:1138, 1984
116. Kittleson M, Keene B, Pion P. Verapamil administration for acute termination of supraventricular tachycardia in dogs. J Am Vet Med Assoc 193(12):1525, 1988
117. Dorian P, Naccarelli GV, Coumel P, et al. A randomized comparison of flecainide versus verapamil in paroxysmal supraventricular tachycardia. Am J Cardiol 77:89A, 1996
118. Singh BN. Controlling cardiac arrhythmias with calcium channel blockers. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 466
119. Ruffy R. Atrial fibrillation. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1995, p 682
120. Böhm M, Schwinger RHG, Erdmann E. Different cardiodepressant potency of various calcium antagonists in human myocardium. Am J Cardiol 65:1039, 1990
121. Roth A, Harrison E, Mitani G, et al. Efficacy of medium and high-dose diltiazem alone and in combination with digoxin for control of heart rate at rest and during exercise in patients with chronic atrial fibrillation. Circulation 73:316, 1986
122. Rodin SM, Johnson BF, Wilson J, et al. Comparative effects of verapamil and isradipine on steady-state digoxin kinetics. Clin Pharmacol Ther 43:668, 1988
123. Piepho RW, Culbertson VL, Rhodes RS. Drug interac-

tions with the calcium-entry blockers. Circulation 75(suppl 5):V181, 1987
124. Salerno DM, Dias VC, Kleiger RE, et al. Efficacy and safety of intravenous diltiazem for treatment of atrial fibrillation and atrial flutter. The diltiazem-atrial fibrillation/flutter study group. Am J Cardiol 63:1046, 1989
124a. Esmolol Multicenter Study Research Group. Efficacy and safety of esmolol vs. propranolol in the treatment of supraventricular tachyarrhythmias: a multicenter double-blind clinical trial. Am Heart J 110:913, 1985
125. Frishman WH. β-Adrenergic blockers. Med Clin North Am 72:37, 1988
126. Yee R, Gulamhusein SS, Klein GJ. Combined verapamil and propranolol for supraventricular tachycardia. Am J Cardiol 53:757, 1984
127. Falk RH, Knowlton AA, Bernard SA, et al. Digoxin for converting recent-onset atrial fibrillation to sinus rhythm. A randomized, double-blinded trial. Ann Intern Med 106:503, 1987
128. Longhurst JC, Ross J Jr. Extracardiac and coronary vascular effects of digitalis. J Am Coll Cardiol 5:99A, 1985
129. Sarter BH, Marchlinski FE. Redefining the role of digoxin in the treatment of arterial fibrillation. Am J Cardiol 69:71G, 1992
130. Camm AJ, Garratt CJ. Adenosine and supraventricular tachycardia. N Engl J Med 325:1621, 1991
131. Moser GH, Schrader J, Deussen A. Turnover of adenosine in plasma of human and dog blood. Am J Physiol 256:C799, 1989
132. Urthaler F, James TN. Effects of adenosine and ATP on AV conduction and on AV junctional rhythm. J Lab Clin Med 79:96, 1972
133. Mitsuoka T, Hirata T, Hiratu N, et al. Comparison of effects of adenosine and ATP on sinus and AV junction rhythms in the canine heart. Jpn Circ J 53:494, 1989
134. Belardinelli L, Mattros EL, Berne RM. Evidence for adenosine mediation of atrioventricular block in the ischemic canine myocardium. J Clin Invest 68:195, 1981
135. Belardinelli L, Pelleg A. Cardiac electrophysiology and pharmacology of adenosine. J Cardiovasc Electrophysiol 1:327, 1990
136. Pelleg A, Belhassen B, Ilia R, et al. Comparative electrophysiologic effects of adenosine triphosphate and adenosine in the canine heart: influence of atropine, propranolol, vagotomy, dipyridamole and aminophylline. Am J Cardiol 55:571, 1985
137. Mauritson DR, Winniford MD, Walker WS, et al. Oral verapamil for paroxysmal supraventricular tachycardia. A long-term, double-blind randomized trial. Ann Intern Med 96:409, 1982
138. Schwartz JB, Keefe D, Kates RE, et al. Acute and chronic pharmacodynamic interaction of verapamil and digoxin in atrial fibrillation. Circulation 65:1163, 1982
139. Grant AO. Propafenone: an effective agent for the management of supraventricular arrhythmias. J Cardiovasc Electrophysiol 7:353, 1996
140. Garcia-Civera R, Sanjuan R, Morell S, et al. Effects of propafenone on induction and maintenance of atrioventricular nodal reentrant tachycardia. PACE 7:649, 1984
141. Chimienti M, Cullen MT Jr, Casadei G. Safety of long-term flecainide and propafenone in the management of patients with symptomatic paroxysmal atrial fibrillation: report from the flecainide and propafenone Italian study investigators. Am J Cardiol 77:60A, 1996
142. Naccarelli GV, Dorian P, Hohnloser SH, et al. Prospective comparison of flecainide versus quinidine for the treatment of paroxysmal atrial fibrillation/flutter. Am J Cardiol 77:53A, 1996
143. Naccarelli GV, Dougherty AH. Amiodarone: a review of its pharmacologic, antiarrhythmic, and adverse effects. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 434
144. UK Propafenone PSVT Study Group. A randomized, placebo-controlled trial of propafenone in the prophylaxis of paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation. Circulation 92:2550, 1995
145. Aarons RD, Molinoff PB. Changes in the density of β-adrenergic receptors in rat lymphocytes, heart and lung after chronic treatment with propranolol. J Pharmacol Exp Ther 221:439, 1982
146. Rango RE, Langlois S. Comparison of withdrawal phenomena after propranolol, metoprolol and pindolol. Br J Clin Pharmacol 13:345S, 1982
147. Smith TW. Digitalis. Mechanisms of action and clinical use. N Engl J Med 318:358, 1988
148. Gillis RA, Quest JA. The role of the nervous system in the cardiovascular effects of digitalis. Pharmacol Rev 31:19, 1979
149. Hoffman BF, Singer DH. Effects of digitalis on electrical activity of cardiac fibers. Prog Cardiovasc Dis 7:226, 1964
150. Bootsma BK, Hoelen AJ, Strackee J, et al. Analysis of the R-R intervals in patients with atrial fibrillation at rest and during exercise. Circulation 41:783, 1970
151. Knowlton AA, Falk RH. Paradoxical increase in heart rate before conversion to sinus rhythm in patients with recent-onset atrial fibrillation. Am J Cardiol 65:930, 1990
152. Falk RH, Leavitt JI. Digoxin for atrial fibrillation: a drug whose time has gone? Ann Intern Med 114:573, 1991
153. Goldman S, Probst P, Selzer A, et al. Inefficacy of therapeutic serum levels of digoxin in controlling the ventricular rate in atrial fibrillation. Am J Cardiol 35:651, 1975
154. Pitcher DW, Papouchado M, James MA, et al. Twenty-four hour ambulatory electrocardiography in patients with chronic atrial fibrillation. Br Med J 29:594, 1986
155. Redfors A. Digoxin dosage and ventricular rate at rest and exercise in patients with atrial fibrillation. Acta Med Scand 190:321, 1971
156. Beasley R, Smith DA, McHaffie DJ. Exercise heart rates of different serum digoxin concentrations in patients with atrial fibrillation. Br Med J 290:9, 1985
157. Zoble RG, Brewington J, Olukotun AY, et al. Comparative effects of nadolol-digoxin combination therapy and digoxin monotherapy for chronic atrial fibrillation. Am J Cardiol 60(suppl):39D, 1987
158. DiBianco R, Morganroth J, Freitag JA, et al. Effects of nadolol on the spontaneous and exercise-provoked heart rate of patients with chronic atrial fibrillation receiving stable dosages of digoxin. Am Heart J 108:1121, 1984
159. Lewis RV, McMurray J, McDevitt DG, et al. Effects of atenolol, verapamil, and xamoterol on heart rate and exercise tolerance in digitalized patients with chronic atrial fibrillation. J Cardiovasc Pharmacol 13:1, 1989
160. Falk RH. Atrial fibrillation. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 803
161. Lundstrom T, Ryden L. Ventricular rate control and exercise performance in chronic atrial fibrillation: ef-

fects of diltiazem and verapamil. J Am Coll Cardiol 16:86, 1990
162. Lang R, Klein H, Segni E, et al. Verapamil improves exercise capacity in chronic atrial fibrillation: double-blind crossover study. Am Heart J 105:820, 1983
163. Lang R, Klein HD, Weiss E, et al. Superiority of oral verapamil therapy to digoxin in treatment of chronic atrial fibrillation. Chest 83:491, 1983
164. Wang Z, Pagé P, Lattel S. Mechanism of flecainide's antiarrhythmic action in experimental atrial fibrillation. Circ Res 71:271, 1992
165. Singh BN. Electrophysiologic basis for the antiarrhythmic actions of sotalol: comparison with other agents. Am J Cardiol 72:8A, 1993
166. Singh BN. Controlling cardiac arrhythmias by lengthening repolarization: historical overview. Am J Cardiol 72:18F, 1993
167. Hondeghen LM, Snyders DJ. Class III antiarrhythmic agents have a lot of potential but a long way to go: reduced effectiveness and dangers of reverse use-dependence. Circulation 81:686, 1990
168. Anderson KP, Walker R, Dustman T, et al. Rate-related electrophysiologic effects of long-term administration of amiodarone on canine ventricular myocardium *in vivo.* Circulation 79:948, 1989
169. Hondeghem LM. Molecular interactions of antiarrhythmic agents with their receptor sites. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1990, p 865
170. Allessie MA, Schalij MJ, Kirchhof CJHJ, et al. Experimental electrophysiology and arrhythmogenicity. Anisotropy and ventricular tachycardia. Eur Heart J 10(suppl):2, 1989
171. Antman EM. Atrial fibrillation and flutter: maintaining stability of sinus rhythm versus ventricular rate control. Part II. J Cardiovasc Electrophysiol 6:962, 1995
172. Kerber RE. Transthoracic cardioversion of atrial fibrillation and flutter: standard techniques and new advances. Am J Cardiol 78:22, 1996
173. Fors WJ, VanderArk CR, Reynolds EW. Evaluation of propranolol and quinidine in the treatment of quinidine-resistant arrhythmias. Am J Cardiol 27:190, 1971
174. Stroobandt R, Stiels B, Hoebrechts R, et al. Propafenone for conversion and prophylaxis of atrial fibrillation. Am J Cardiol 79:418, 1997
175. Anderson JL, Gilbert EM, Alpert BL, et al. Prevention of symptomatic recurrences of paroxysmal atrial fibrillation in patients initially tolerating antiarrhythmic therapy: a multicenter, double-blind, cross-over study of flecainide and placebo using transtelephonic monitoring. Circulation 80:1557, 1989
176. Tieleman RG, Gosselink AT, Crijns HJGM, et al. Efficacy, safety, and determinants of conversion of atrial fibrillation and flutter with oral amiodarone. Am J Cardiol 79:53, 1997
177. Anderson JL. Acute treatment of atrial fibrillation and flutter. Am J Cardiol 78:17, 1996
178. Hellestrand KJ. Intravenous flecainide acetate for supraventricular tachycardias. Am J Cardiol 62:16D, 1988
179. Hellestrand KJ. Efficacy and safety of long-term oral flecainide acetate in patients with responsive supraventricular tachycardia. Am J Cardiol 77:83A, 1996
180. Alboni P, Paparella N, Cappato R, et al. Direct and autonomically mediated effects of oral flecainide. Am J Cardiol 61:759, 1988
181. Capucci A, Villani GQ, SATE Group. Propafenone oral loading dose plus digitalis in converting atrial fibrillation to sinus rhythm: a placebo-controlled multicenter study. Abstract. Circulation 92:1775, 1995
182. Passmore JM, Rinkenberger RL, Giebel RA, et al. Amiodarone: predictors of clinical response in atrial flutter and atrial fibrillation. Abstract. J Am Coll Cardiol 7:83A, 1986
183. Kerin NZ, Ansari-Leesar M, Fitel K, et al. The effectiveness and safety of the simultaneous administration of quinidine and amiodarone in the conversion of chronic atrial fibrillation. Am Heart J 125:1017, 1993
184. Antman EM. Maintaining sinus rhythm with antifibrillatory drugs in atrial fibrillation. Am J Cardiol 78:67, 1996
185. Middlekauff HR, Wiener I, Stevenson WG. Low-dose amiodarone for atrial fibrillation. Am J Cardiol 72:75F, 1993
186. Ellenbogen KA, Clemo HF, Stambler BS, et al. Efficacy of ibutilide for termination of atrial fibrillation and flutter. Am J Cardiol 78:42, 1996
187. Naccarelli GV, Lee KS, Gibson JK, et al. Electrophysiology and pharmacology of ibutilide. Am J Cardiol 78:12, 1996
188. Kay GN, Epstein AE, Dailey SM, et al. Selective radiofrequency ablation of the slow pathway for the treatment of atrioventricular nodal reentrant tachycardia. Circulation 85:1675, 1992
189. Wu D, Weh S, Wang C, et al. A simple technique for selective radiofrequency ablation of the slow pathway in atrioventricular node reentrant tachycardia. J Am Coll Cardiol 21:1612, 1993
190. Wu D, Hung J, Kuo C, et al. Effects of quinidine on atrioventricular nodal reentrant paroxysmal tachycardia. Circulation 64:823, 1981
191. Shenasa M, Gilbert CJ, Schmide DH, et al. Procainamide and retrograde atrioventricular nodal conduction in man. Circulation 65:355, 1982
192. Niazi I, Naccarelli G, Dougherty A, et al. Treatment of atrioventricular node reentrant tachycardia with encainide: reversal of drug effect with isoproterenol. J Am Coll Cardiol 13:904, 1989
193. Harrison DC, Bottorff MB. Basic principles of pharmacokinetics: antiarrhythmic drugs. *In* Sperelakis N (ed): Physiology and Pathophysiology of the Heart. 3rd ed. Norwell, MA, Kluwer Academic Publishers, 1995, p 565
194. de Madron E, Kadish A, Spear JF, et al. Incessant atrial tachycardias in a dog with tricuspid dysplasia. J Vet Intern Med 1:163, 1987
195. Kornreich BG, Moïse NS. Right atrioventricular valve malformation in dogs and cats: an electrocardiographic survey with emphasis on splintered QRS complexes. J Vet Intern Med 11:226, 1997
196. El-Sherif N. Reentrant mechanisms in ventricular arrhythmias. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1995, p 567
197. Kadish A, Morady F. Mechanism-specific therapy of ventricular tachycardia. J Cardiovasc Electrophysiol 1:688, 1990
198. Hondeghem LM. Class II agents: amiodarone, bretylium, and sotalol. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1995, p 1330
199. Link MS, Homoud M, Foote CB, et al. Antiarrhythmic drug therapy for ventricular arrhythmias: current perspectives. J Cardiovasc Electrophysiol 7:653, 1996
200. CAST Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 321:406, 1989
201. CAST Trial II Investigators. Effect of the antiarrhythmic

agent moricizine on survival after myocardial infarction. N Engl J Med 327:227, 1992
202. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 327:227, 1992
203. Vaughan Williams EM. Classification of antiarrhythmic drugs. *In* Sand E, Flenstedt-Jensen E, Olesen KH (eds): Symposium on Cardiac Arrhythmias. Sodertalje, Sweden, AB Astra, 1970, p 440
204. Singh BN, Vaughan Williams EM. A fourth class of antidysrhythmic action. Effect of verapamil on ouabain toxicity, on atrial and ventricular intracellular potentials, and on other features of cardiac function. Cardiovasc Res 6:109, 1972
205. Josephson ME. Evaluation of antiarrhythmic agents. *In* Clinical Cardiac Electrophysiology Techniques and Interpretations. Philadelphia, Lea & Febiger, 1993, p 630
206. Sicilian Gambit Members. Antiarrhythmic Therapy: A Pathophysiologic Approach. Mount Kisco, NY, Futura Publishing Company, 1994
207. Task Force Working Group on Arrhythmias of the European Society of Cardiology. The Sicilian Gambit: A new approach to the classification of drugs based on the actions of antiarrhythmic mechanisms. Circulation 84:1831, 1991
208. Campbell TJ. Subclassification of class I antiarrhythmic drugs: enhanced relevance after CAST. Cardiovasc Drug Ther 6:519, 1992
209. Bigger JT, Hoffman BF. Antiarrhythmic drugs. *In* Goodman AG, Rall TW, Nies AS, et al (eds): The Pharmacologic Basis of Therapeutics. New York, Pergamon Press, 1990, p 840
210. Schwartz PJ, Priori SG. Sympathetic nervous system and cardiac arrhythmias. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1990, p 303
211. Smith ML, Ellenbogen KA, Beightol LA, et al. Sympathetic neural responses to induced ventricular tachycardia. J Am Coll Cardiol 18:1015, 1991
212. Lucchesi BR, Chi L, Friedrichs GS, et al. Antiarrhythmic versus antifibrillatory actions: interference from experimental studies. Am J Cardiol 72:25F, 1993
213. Meredith IT, Broughton A, Jennings GL, et al. Evidence of a selective increase in cardiac sympathetic activity in patients with sustained ventricular arrhythmias. N Engl J Med 325:618, 1991
214. Zipes DP, Miyazaki T. The autonomic nervous system and the heart: basis for understanding interactions and effects on arrhythmia development. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1990, p 312
215. Grant AO, Whalley DW, Wendt DJ. Pharmacology of the cardiac sodium channel. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1995, p 247
216. Nilius B, Tytgat J, Albitz R. Atrionatriuretic peptide transforms cardiac sodium channels into calcium-conducting channels. Science 247:969, 1990
217. Feldman T, Carroll JD, Munkenbeck F, et al. Hemodynamic recovery during simulated ventricular tachycardia: role of adrenergic receptor activation. Am Heart J 115:576, 1988
218. Podrid PJ, Venditti FJ, Levine PA, et al. The role of exercise testing in evaluation of arrhythmias. Am J Cardiol 62:24H, 1988
219. Calkins H, Sousa J, El-Atassi R, et al. Reversal of antiarrhythmic drug effects by epinephrine: quinidine versus amiodarone. J Am Coll Cardiol 19:347, 1992
220. Singh BN. Antiarrhythmic actions of amiodarone: a profile of a paradoxical agent. Am J Cardiol 78:41, 1996
221. Sanguinetti MC, Jurkiewicz NK, Scott A, et al. Isoproterenol antagonizes prolongation of refractory period by the class III antiarrhythmic agent E-4031 in guinea pig myocytes. Circ Res 68:77, 1991
222. ESVEM investigators–Mason JW. A comparison of seven antiarrhythmic drugs in patients with ventricular tachyarrhythmias. N Engl J Med 329:452, 1993
223. Waldo AL, Camm AJ, deRuyter H, et al. Preliminary mortality results from the survival with oral *d*-sotalol (SWORD) trial. Abstract. J Am Coll Cardiol 15A, 1995
224. Waldo AL, Camm AJ, deRuyter H, et al. Survival with oral *d*-sotalol in patients with left ventricular dysfunction after myocardial infarction: rationale, design, and methods (the SWORD trial). Am J Cardiol 75:1023, 1995
225. Kolettis TM, Saksena S, Mathew P, et al. Right and left ventricular hemodynamic performance during sustained ventricular tachycardia. Am J Cardiol 79:323, 1997
226. Buxton AE, Marchlinski FE, Waxman HL, et al. Prognostic factors in nonsustained ventricular tachycardia. Am J Cardiol 53:1275, 1984
227. Oseran DS, Gang ES, Rosenthal ME, et al. Electropharmacologic testing in sustained ventricular tachycardia associated with coronary heart disease: value of the response to intravenous procainamide in predicting the response to oral procainamide and oral quinidine treatment. Am J Cardiol 56:883, 1985
228. Singh SN. Congestive heart failure and arrhythmias: therapeutic modalities. J Cardiovasc Electrophysiol 8:89, 1997
229. Harpster NK. Boxer cardiomyopathy. *In* Kirk RW (ed): Current Veterinary Therapy VII. Philadelphia, WB Saunders, 1980, p 329
230. Moïse NS, Meyers-Wallen V, Flahive WJ, et al. Inherited ventricular arrhythmias and sudden death in German shepherd dogs. J Am Coll Cardiol 24:233, 1994
231. Moïse NS, Gilmour RF Jr, Riccio ML. An animal model of sudden arrhythmic death. J Cardiovasc Electrophysiol 8:98, 1997
232. Moïse NS, Gilmour RF Jr, Riccio ML, et al. Diagnosis of inherited ventricular tachycardia in German shepherd dogs. Am J Vet Med Assoc 210:403, 1997
233. Moïse NS, Riccio MJ, Flahive WJ, et al. Age-dependent development of ventricular arrhythmias in a spontaneous animal model of sudden cardiac death. Cardiovasc Res 34:483, 1997
234. Morganroth J, Michelson EL, Horowitz LN, et al. Limitations of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency. Circulation 58:408, 1978
235. Morganroth J. Ambulatory Holter electrocardiography: choice of technologies and clinical uses. Ann Intern Med 2:73, 1985
236. Morganroth J. Indications for antiarrhythmic suppression of ventricular arrhythmias: a definition of life-threatening ventricular arrhythmias. Am J Cardiol 72:3A, 1993
237. Toivonen L. Spontaneous variability in the frequency of ventricular premature complexes over prolonged intervals and implications for antiarrhythmic treatment. Am J Cardiol 60:608, 1987
238. Takada H, Mikawa T, Murayama M, et al. Range of ventricular ectopic complexes in healthy subjects studied with repeated ambulatory electrocardiographic recordings. Am J Cardiol 63:184, 1989

239. Pratt CM, Delclos G, Wierman AM, et al. The changing base line of complex ventricular arrhythmias: a new consideration in assessing long-term antiarrhythmic drug therapy. N Engl J Med 313:1444, 1985
240. Raeder EA, Hohnloser SH, Graboys TB, et al. Spontaneous variability and circadian distribution of ectopic activity in patients with malignant ventricular arrhythmia. J Am Coll Cardiol 12:656, 1988
241. Reiffel JA. Implications of the electrophysiologic study versus electrocardiographic monitoring trial for controlling ventricular tachycardia and fibrillation. Am J Cardiol 78:34, 1996
242. Gorgels APM, van den Dool A, Hofs A, et al. Comparison of procainamide and lidocaine in terminating sustained monomorphic ventricular tachycardia. Am J Cardiol 78:43, 1996
243. Roden DM. Role of the electrocardiogram in determining electrophysiologic end points of drug therapy. Am J Cardiol 62:34H, 1988
244. Kay GN, Plumb VJ, Arciniegas JG, et al. Torsades de pointes: the long–short initiating sequence and other clinical features: observations in 32 patients. J Am Coll Cardiol 2:806, 1983
245. Surawicz B, Knoebel SB. Long QT: good, bad, or indifferent? J Am Coll Cardiol 4:398, 1984
246. Antzelevitch C, Sicouri S, Lukas A, et al. Regional differences in electrophysiology of ventricular cells: physiological and clinical implications. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1995, p 228
247. Roden DM. New concepts in antiarrhythmic drug pharmacokinetics. *In* Zipes D (ed): Symposium on New Therapeutic Approaches to Cardiac Arrhythmias. Philadelphia, Lea & Febiger, 1987, p 19
248. Roden DM. Risk and benefits of antiarrhythmic therapy. N Engl J Med 331:785, 1994
249. Woosley RL. Role of plasma concentration monitoring in the evaluation of response to antiarrhythmic drugs. Am J Cardiol 62:9H, 1988
250. Campbell NPS, Kelley JB, Adgey AAJ, et al. The clinical pharmacology of mexiletine. Br J Clin Pharmacol 6:103, 1978
251. Adams PC, Holt DW, Storey GC, et al. Amiodarone and its desethyl metabolite: tissue distribution and morphologic changes during long-term therapy. Circulation 72:1064, 1985
252. Pourbaix S, Berger Y, Desager JP, et al. Absolute bioavailability of amiodarone in normal subjects. Clin Pharmacol Ther 37:118, 1985
253. Greenberg ML, Lerman BB, Shipe JR, et al. Relationship between amiodarone and desethylamiodarone plasma concentrations and electrophysiologic effects, efficacy, and toxicity. J Am Coll Cardiol 9:1148, 1987
254. Falik R, Flores BT, Shaw L, et al. Relationship of steady-state serum concentrations of amiodarone and desethylamiodarone to therapeutic efficacy and adverse effects. Am J Med 82:1102, 1987
255. Talajic M, DeRoode MR, Nattel S. Comparative electrophysiologic effects of intravenous amiodarone and desethyl amiodarone in dogs: evidence for clinically relevant activity of the metabolite. Circulation 75:265, 1987
256. Zipes DP, Prystowsky EN, Heger JJ. Electrophysiologic testing of antiarrhythmic agents. Am Heart J 103:610, 1982
257. Woosley RL, Roden M. Importance of metabolites in antiarrhythmic therapy. Am J Cardiol 52:3C, 1983
258. Singh BN. Choice and chance in drug therapy of cardiac arrhythmias: technique versus drug-specific responses in evaluation of efficacy. Am J Cardiol 72:114F, 1993
259. Singh BN, Wellens HJJ, Hiraoka M (eds). Electropharmacological Control of Cardiac Arrhythmias: To Delay Conduction or to Prolong Refractoriness? Mt. Kisco, NY, Futura Publishing Company, 1994, p 1
260. Campbell RWF. Class 1B antiarrhythmic agents. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 391
261. Roth A, Malov N, Bloch Y, et al. Usefulness of self-administration of intramuscular lidocaine in the prehospital setting for ventricular tachyarrhythmias unassociated with acute myocardial infarction; the "Shahal" experience in Israel. Am J Cardiol 79:611, 1997
262. Ryden L, Waldenstrom A, Eho L, et al. Comparison between effectiveness of intramuscular and intravenous lidocaine on ventricular arrhythmias complicating acute myocardial infarction. Br Heart J 35:1124, 1973
263. Stanton MS. Class 1 antiarrhythmic drugs: quinidine, procainamide, disopyramide, lidocaine, mexiletine, tocainide, phenytoin, moricizine, flecainide, propafenone. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1995, p 1296
264. Beltrame J, Aylward PE, McRitchie RJ, et al. Comparative haemodynamic effects of lidocaine, mexiletine, and disopyramide. J Cardiovasc Pharmacol 6:484, 1984
265. Darby S, Bennett MA, Cruickshank JC, et al. Trial of combined intramuscular and intravenous lignocaine in prophylaxis of ventricular tachyarrhythmias. Lancet 1:817, 1972
266. Roos JC, Dunning AJ. Effects of lidocaine on impulse formation and conduction defects in man. Am Heart J 89:686, 1975
267. Rosen MR, Strauss H, Janse MJ. The classification of antiarrhythmic drugs. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1995, p 1277
268. Roden DM. Ionic mechanisms for prolongation of refractoriness and their proarrhythmic and antiarrhythmic correlates. Am J Cardiol 78:12, 1996
269. Singh BN. The coming of age of the class III antiarrhythmic principle: retrospective and future trends. Am J Cardiol 78:17, 1996
270. Campbell TJ. Differing electrophysiological effects of class 1a, 1b, and 1c antiarrhythmic drugs on guinea-pig sinoatrial node. Br J Pharmacol 91:395, 1987
271. Abrahamsson C, Carlson L, Duker G. Lidocaine and nisoldipine attenuate almokalant-induced dispersion of repolarization and early afterdepolarizations *in vitro*. J Cardiovasc Electrophysiol 7:1074, 1996
272. Arnsdorf MF, Bigger JT. Effect of lidocaine hydrochloride on membrane conductance in mammalian cardiac Purkinje fibers. J Clin Invest 51:2253, 1972
273. Strichartz GR. The inhibition of sodium currents in myelinated nerve by quaternary derivatives of lidocaine. J Gen Physiol 62:37, 1973
274. Anderson JL. Reassessment of benefit-risk ratio and treatment algorithms for antiarrhythmic therapy after the Cardiac Arrhythmia Suppression Trial. J Clin Pharmacol 30:981, 1990
275. Allen JD, Dressman FJ, Wit AL. Actions of lidocaine on transmembrane potentials of subendocardial Purkinje fiber surviving in infarcted canine heart. Circ Res 43:470, 1978
276. LeMarec H, Dangman KH, Danilo P, et al. An evaluation of automaticity and triggered activity in the canine

heart one to four days after myocardial infarction. Circ Res 71:1224, 1985
277. Marcus FI, Opie LH. Antiarrhythmic agents. *In* Opie LH (ed): Drugs for the Heart. Philadelphia, WB Saunders, 1995, p 207
278. Schmidt C, Kadish AH, Balke WC, et al. Cycle length-dependent effects on normal and abnormal intraventricular electrocardiograms: effect of procainamide. Am J Cardiol 12:395, 1988
279. Giardina EGV, Lipka LJ. Class 1A antiarrhythmic agents: quinidine, procainamide, disopyramide. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 369
280. Morady F, Di Carlo LA, de Buitleir M, et al. Effects of incremental doses of procainamide on ventricular refractoriness, intraventricular conduction, and induction of ventricular tachycardia. Circulation 74:1355, 1986
281. Nademanee K, Singh BN, Stevenson WG, et al. Amiodarone and post-MI patients. Circulation 88(2):764, 1993
282. Gloor HO, Urthaler F, James TN. Acute effects of amiodarone upon the canine sinus node and atrioventricular junction region. J Clin Invest 71:1457, 1983
283. Patterson E, Eller BT, Abrams GD, et al. Ventricular fibrillation in a conscious canine preparation of sudden coronary death: prevention by short- and long-term amiodarone administration. Circulation 68:857, 1983
284. Patterson E, Lynch JJ, Lucchesi BR. Antiarrhythmic and antifibrillatory actions of the β-adrenergic receptor antagonist, *d,l*-sotalol. J Pharmacol Exp Ther 230:519, 1984
285. Hession M, Blum R, Podrid PJ, et al. Mexiletene and tocainide: does response to one predict response to the other? J Am Coll Cardiol 7:338, 1986
286. Singh S, Klein R, Eisenberg B, et al. Long-term effect of mexiletine on left ventricular function and relation to suppression of ventricular arrhythmia. Am J Cardiol 66:1222, 1990
287. O'Callaghan PA, McGovern BA. Evolving role of sotalol in the management of ventricular tachyarrhythmias. Am J Cardiol 78:54, 1996
288. Hanyok JJ, MacNeil DJ. Sotalol versus class I and II antiarrhythmic agents. Cardiovasc Drugs Ther 4(suppl):603, 1990
289. Frishman WH. Clinical Pharmacology of the β-Adrenoreceptor Blocking Drugs. Norwalk, Appleton-Century-Crofts, 1984
290. Steinbeck G, Anderson D, Bach P, et al. A comparison of electrophysiologically guided antiarrhythmic drug therapy with β-blocker therapy in patients with symptomatic, sustained ventricular tachyarrhythmias. N Engl J Med 372:987, 1992
291. Reiffel JA, Hahn E, Hartz V, et al. Sotalol for ventricular tachyarrhythmias: β-blocking and class III contributions, and relative efficacy versus class I drugs after prior drug failure. Am J Cardiol 79:1048, 1997
292. Anderson J, Lutz JR, Gilbert EM, et al. A randomized trial of low dose β-blockade therapy for idiopathic dilated cardiomyopathy. Am J Cardiol 55:471, 1985
293. Frishman WH, Cavusoglu E. β-Adrenergic blockers and their role in the therapy of arrhythmias. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 421
294. Frishman W, Jacob H, Eisenberg E, et al. Clinical pharmacology of the new β-adrenergic blocking drugs. Part 8: Self poisoning with β-adrenoceptor blocking drugs: recognition and management. Am Heart J 98:798, 1979
295. Nakaya H, Kimura S, Nakao Y, et al. Effects of nipradilol (K-351) on the electrophysiological properties of canine cardiac tissues: comparison with propranolol and sotalol. Eur J Pharmacol 104:335, 1984
296. CASCADE Investigators—Greene HL. The CASCADE study: randomized antiarrhythmic drug therapy in survivors of cardiac arrest in Seattle. Am J Cardiol 72:70F, 1993
297. CASCADE Investigators. Randomized antiarrhythmic drug therapy in survivors of cardiac arrest (the CASCADE study). Am J Cardiol 72:280, 1993
298. Nora M, Zipes D. Empiric use of amiodarone and sotalol. Am J Cardiol 72:62F, 1993
299. Amiodarone vs. Sotalol Study Group. Multicentric randomized trial of sotalol vs. amiodarone for chronic malignant ventricular tachyarrhythmias. Eur Heart J 10:685, 1989
300. Roden DM. Pharmacokinetics of amiodarone: implications for drug therapy. Am J Cardiol 72:45F, 1993
301. Kato R, Ikeda N, Yabek SM, et al. Electrophysiologic effects of the levo- and dextrorotatory isomers of sotalol in isolated cardiac muscle and their *in vivo* pharmacokinetics. J Am Coll Cardiol 7:116, 1986
302. Hanyok JJ. Clinical pharmacokinetics of sotalol. Am J Cardiol 72:19A, 1993
303. Gomoll AW, Lekich RF, Bartek MJ, et al. Comparability of the electrophysiologic responses and plasma and myocardial tissue concentrations of sotalol and its *d*-stereoisomer in the dog. J Cardiovasc Pharmacol 16:204, 1990
304. Mostow ND, Rakita L, Vrobel TR, et al. Amiodarone correlation of serum concentration with suppression of complex ventricular ectopic activity. Am J Cardiol 54:569, 1983
305. Rotmensch HH, Belhassen B, Swanson BN, et al. Steady-state serum amiodarone concentrations: relationships with antiarrhythmic efficacy and toxicity. Ann Intern Med 101:462, 1984
306. Charlier R, Delaunois G, Bauthier J. Recherche dans la serie des benzofurannes. XL. Propriété antiarrhythmiques de l'amiodarone. Cardiologia 54:83, 1969
307. Nattel S, Talajic M, Fermani B, et al. Amiodarone: pharmacology, clinical actions, and relationship between them. J Cardiovasc Electrophysiol 3:266, 1992
308. Woosley RL, Barbey JT, Wang T, et al. Concentration/response relations for the multiple antiarrhythmic actions of sotalol. Am J Cardiol 65(suppl):22A, 1990
309. Campbell RWF, Furniss SS. Practical considerations in the use of sotalol for ventricular tachycardia and ventricular fibrillation. Am J Cardiol 72:80A, 1993
310. Hamer AWF, Arkles LB, Johns JA. Beneficial effects of low dose amiodarone in patients with congestive heart failure: a placebo control trial. J Am Coll Cardiol 14:1768, 1989
311. Day CP, McComb JM, Matthews J, et al. Reduction in QT dispersion by sotalol following myocardial infarction. Eur Heart J 67:511, 1991
312. Corr PB, Gross RW, Sobel BE. Amphipathic metabolites and membrane dysfunction in ischemic myocardium. Circ Res 55:135, 1984
313. Nademanee K, Singh BN, Hendrickson JA, et al. Pharmacokinetic significance of serum reverse T_3 levels during amiodarone treatment: a potential method for monitoring chronic drug therapy. Circulation 66:202, 1982
314. Foster MT, Peter RW, Froman D, et al. Electrophysio-

logic effects and predictors of success of combination therapy with class Ia and Ib antiarrhythmic drugs for sustained ventricular arrhythmias. Am J Cardiol 78:47, 1996
315. Duff HJ. Mexiletine-quinidine combination: enhanced antiarrhythmic and electrophysiologic activity in the dog. J Pharmacol Exp Ther 249:617, 1989
316. Costard-Jaeckle A, Liem LB, et al. Frequency-dependent effect of quinidine, mexiletine and their combination on post-repolarization refractoriness *in vivo*. J Cardiovasc Pharmacol 14:810, 1989
317. Duff HJ. Antiarrhythmic drug combination therapy. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 498
318. Duff HJ, Cannon NJ, Sheldon RS. Mexiletine-quinidine in isolated hearts: an interaction involving the sodium channel. Cardiovasc Res 23:584, 1989
319. Duff HJ, Rahmberg J, Sheldon RS. Role of quinidine in the mexiletine-quinidine interaction: electrophysiologic correlates of enhanced antiarrhythmic efficacy. J Cardiovasc Pharmacol 16:685, 1990
320. Duff HJ, Roden D, Primm RK, et al. Mexiletine in the treatment of resistant ventricular arrhythmias: enhancement of efficacy and reduction of dose-related side effects of combination with quinidine. Circulation 67:1124, 1983
321. Lee SD, Newman D, Ham M, et al. Electrophysiologic mechanisms of antiarrhythmic efficacy of a sotalol and class Ia drug combination: elimination of reverse use-dependence. J Am Coll Cardiol 29:100, 1997
322. Brodsky MA, Chough SP, Allen BJ, et al. Adjuvant metoprolol improves efficacy of class I antiarrhythmic drugs in patients with inducible sustained monomorphic ventricular tachycardia. Am Heart J 124:629, 1992
323. Bennett PB, McKinney L, Begenisich T, et al. Adrenergic modulation of the delayed rectifier potassium channel in calf cardiac Purkinje fibers. Biophys J 49:839, 1986
324. Singh BN, Vaughan Williams EM. Effect of altering potassium concentrations on the action of lidocaine and diphenylhydantoin on rabbit atrial and ventricular muscle. Circ Res 29:286, 1971
325. Campbell TJ. Kinetics of onset of rate-dependent effects of class I antiarrhythmic drugs are important in determining their effects on refractoriness in guinea-pig ventricle and provide a theoretical basis for this subclassification. Cardiovasc Res 17:344, 1983
326. Podrid PJ. Aggravation of arrhythmia by antiarrhythmic drugs. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 507
327. Coplen SE, Antman EM, Berlin JA, et al. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion: a meta-analysis of randomized control trials. Circulation 82:1106, 1986
328. Morganroth J, Goin JE. Quinidine-related mortality in the short-to-medium-term treatment of ventricular arrhythmias: a meta-analysis. Circulation 84:1977, 1991
329. Morganroth J, Horowitz LN. Flecainide—its proarrhythmic effect and expected changes on the surface electrocardiogram. Am J Cardiol 53:893, 1984
330. Podrid PJ, Lambert S, Graboys TB, et al. Aggravation of arrhythmia by antiarrhythmic drugs—incidence and predictors. Am J Cardiol 59:38E, 1987
331. Slater WB, Lampert S, Podrid PJ, et al. Clinical predictors of arrhythmia worsening by antiarrhythmic drugs. Am J Cardiol 61:349, 1988
332. Hii JT, Wyse DG, Gillis AM, et al. Precordial QT interval dispersion as a marker of torsades de pointes. Disparate effects of class Ia antiarrhythmic drugs and amiodarone. Circulation 96:1376, 1992
333. Dessertenne F. La tachycardia ventriculaire à deux foyers opposés variables. Arch Mal Coeur 59:263, 1966
334. Calvert CA, Jacobs GJ, Pickus CW. Bradycardia-associated episodic weakness, syncope, and aborted sudden death in cardiomyopathic Doberman pinschers. J Vet Intern Med 10:88, 1996
335. Calvert CA, Pickus CW, Jacobs GJ. Efficacy and toxicity of tocainide for the treatment of ventricular tachyarrhythmias in Doberman pinschers with occult cardiopathy. J Vet Intern Med 10:234, 1996
336. Brittain D, Concannon PW, Flanders JA, et al. Use of surgical intrauterine insemination to manage infertility in a colony of research German shepherd dogs. J Lab Anim Sci 45:404, 1995
337. Dae M, Ursell P, Lee R, Stilson C, et al. Heterogeneous sympathetic innervation in German shepherd dogs with inherited ventricular arrhythmias and sudden death. Circulation 96:1337, 1997
338. Freeman LC, Pacioretty LM, Moïse NS, et al. Decreased density of I_{to} in left ventricular myocytes from German shepherd dogs with inherited arrhythmias. J Cardiovasc Electrophysiol 8:87, 1997
339. Gilmour RF Jr, Moïse NS. Triggered activity as a mechanism for inherited ventricular arrhythmias in German shepherd dogs. J Am Coll Cardiol 27:1526, 1996
340. Moïse NS, Moon PF, Flahive WJ, et al. Phenylephrine-induced ventricular arrhythmias in dogs with inherited sudden death. J Cardiovasc Electrophysiol 7:217, 1996
341. Doval HC, Nul DR, Grancelli HO, et al. Nonsustained ventricular tachycardia in severe heart failure. Circulation 94:3198, 1996
342. Singh BN, Fletcher RD, Fisher G, et al. Therapy in congestive heart failure. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. N Engl J Med 333:77, 1995
343. Hansen DE, Craig CS, Hondeghem LM. Stretch-induced arrhythmias in the isolated canine ventricle: evidence for the importance of mechanoelectrical feedback. Circulation 81:1094, 1990
344. Franz MR, Cima R, Wang D, et al. Electrophysiological effects of myocardial stretch and mechanical determinants of stretch-activated arrhythmias. Circulation 86:968, 1992
345. Gomes JA, Mehta D, Ip J, et al. Predictors of long-term survival in patients with malignant ventricular arrhythmias. Am J Cardiol 79:1054, 1997
346. Ward DE, Camm AJ. Dangerous ventricular arrhythmias—can we predict drug efficacy? N Engl J Med 329:498, 1993
347. Anastasiou-Nana MI, Menlove RL, Nanas JN, et al. Spontaneous variability of ventricular arrhythmias in patients with chronic heart failure. Am Heart J 122:1007, 1991
348. Reiffel JA. Normal sinus rhythm and its variants (sinus arrhythmia, sinus tachycardia, sinus bradycardia, sinus node reentry, and sinus node dysfunction [sick sinus syndrome]): mechanism, recognition, and management. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 752
349. Tilley LP. Essentials of Canine and Feline Electrocardiography. Interpretation and Treatment. 3rd ed. Philadelphia, WB Saunders, 1992, p 184
350. Bonke FIM, Kirckhoff CJHJ, Allessie MA, et al. Impulse

propagation from the SA node to the ventricles. Experimentia 43:1044, 1987
351. Benditt DB, Sakaguchi S, Goldstein MA, et al. Sinus node dysfunction: pathophysiology, clinical features, evaluation, and treatment. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. 2nd ed. Philadelphia, WB Saunders, 1995, p 1215
352. Sutton R, Kenny RA. The natural history of sick sinus syndrome. PACE 9:1110, 1986
353. Jordan JA, Yamaguchi I, Mandel WJ. Studies on the mechanism of sinus node dysfunction in the sick sinus syndrome. Circulation 57:217, 1978
354. Jose AD, Collison D. The normal range and the determinants of the intrinsic heart rate in man. Cardiovasc Res 4:160, 1970
355. Kugo K, Yamaguchi I, Sugishita Y, et al. Assessment by autonomic blockade of age-related changes of the sinus node function and autonomic regulation in sick sinus syndrome. Am J Cardiol 61:361, 1988
356. Strauss HC, Prykstowsky EN, Scheinman MM. Sinoatrial and atrial electrogenesis. Prog Cardiovasc Dis 19:3:85, 1977
357. Becker AE. General comments. *In* Bonke FIM (ed): The Sinus Node. Structure, Function, and Clinical Relevance. The Hague, The Netherlands, Martinus Nijhoff, 1978, p 212
358. Opthof T, de Tonge B, Jongsma HJ, et al. Functional morphology of mammalian sinoatrial node. Eur Heart J 8:1249, 1987
359. Davies MJ, Pomerance A. Quantitative study of aging changes in the human sinoatrial node and internodal tract. Br Heart J 34:150, 1972
360. Reiffel JA. Electrophysiologic evaluation of sinus node function. Cardiol Clin 4:401, 1986
361. Reiffel JA, Ferrick K, Zimmerman J, et al. Electrophysiologic studies of the sinus node and atria. Cardiovasc Clin 16:37, 1985
362. Reiffel JA. Clinical electrophysiology of the sinus node in man. Prog Clin Biol Res 275:239, 1988
363. Kocovic Z, Friedman PL. Atrioventricular nodal block. *In* Podrid PJ, Kowey PR (eds): Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. Baltimore, Williams & Wilkins, 1995, p 1039
364. Alboni P, Menozzi C, Brignole M, et al. Effects of permanent pacemaker and oral theophylline in sick sinus syndrome. The THEOPACE study: a randomized controlled trial. Circulation 96:262, 1997

19

Diagnosis and Management of Feline Arrhythmias

PHILIP R. FOX

NEIL K. HARPSTER

CLINICAL OVERVIEW

Arrhythmias are often detected during evaluation and management of feline heart disease.[1–6] In some cases they may constitute the principal focus of therapy (e.g., slow the ventricular rate in atrial fibrillation; reverse symptomatic bradycardia from complete atrioventricular block with pacemaker therapy; suppress electrically or hemodynamically unstable tachyarrhythmias). Other conditions require only electrocardiographic monitoring to uncover arrhythmias that may require future therapy. Arrhythmias may completely resolve when the inciting disorder is identified and corrected (chapters 28, 33, 34).[6–10]

Although feline arrhythmias are generally similar to those reported in dogs,[11, 12] their relative frequency and clinical significance may be dissimilar. Acquired cardiovascular diseases affecting dogs and cats are markedly different. For example, myocardial diseases most commonly affect cats, especially hypertrophic or restrictive cardiomyopathy (chapter 28). In contrast, dogs acquire myxomatous valvular degeneration (chronic atrioventricular valve insufficiency), dilated cardiomyopathy, or heartworm disease. Accordingly, these disorders influence the electrocardiagram (ECG) and related therapies.

CONDITIONS ASSOCIATED WITH ARRHYTHMIAS

Arrhythmias may be associated with cardiac as well as extracardiac diseases. Comparison of arrhythmia incidence between dogs and cats has not been reported. However, it is our experience that cats have a lower incidence of clinically significant arrhythmias compared with dogs.

CONGENITAL HEART DISEASE

Arrhythmias are not usually observed with congenital heart disease unless malformations are severe, pressure or volume overloads are significant, cardiomegaly is advanced, or congestive heart failure is present.[5, 13] Some

TABLE 19–1

Frequency of Cardiac Arrhythmias: Comparison of Feline Populations with Cardiomyopathy, Congestive Heart Failure, and Thromboembolism*

		Arrhythmia Type							
		Supraventricular			*Ventricular*			*AV Node Abnormalities*	
Cardiomyopathy	Total	*SVPC*	*PSVT*	*AF*	*VPCs*	*PVTachy*	*Sinus Node Abnormalities*	*1°/2°*	*3° AVB*
Hypertrophic	205	10 (4.9)†	8 (3.9)†	4 (2.0)†	19 (9.3)†	5 (2.4)†	3 (1.5)†		
with CHF	74	5 (6.8)	2 (2.7)	1 (1.4)	11 (14.9)	3 (4.1)	2 (2.7)		
with TBE	32	3 (9.4)	1 (3.1)	3 (9.4)	10 (31.3)	1 (3.1)			
with CHF & TBE	18	3 (16.7)			6 (33.3)				
Intermediate‡	128	12 (9.4)	7 (5.5)	5 (3.9)	33 (25.8)	3 (2.3)	2 (1.6)	2 (1.6) 1 (2.1)	2 (1.6) 2 (4.3)
with CHF	47	7 (14.9)	2 (4.3)	1 (2.1)	18 (38.3)	2 (4.3)			
with TBE	19	3 (15.8)	2 (10.5)		5 (26.3)	2 (10.5)			
with CHF & TBE	8	3 (37.5)	1 (12.5)		5 (62.5)				
Dilatative	84	6 (7.1)	13 (15.5)	2 (2.4)	14 (16.7)	6 (7.1)	1 (1.2)		
with CHF	54	4 (7.4)	11 (20.4)	1 (1.9)	9 (16.7)	1 (1.9)			
with TBE	3					2 (66.7)			

*Consecutive feline cases, Angell Memorial Animal Hospital (1985–1991).
†Numbers in parentheses are the percent of cats in each group having that arrhythmia.
‡Intermediate cardiomyopathy is a classification of myocardial disease used by NK Harpster; it includes disorders similar to Restrictive Cardiomyopathy (chapter 28).
SVPC, supraventricular premature complexes; PSVT, paroxysmal supraventricular tachycardia; AF, atrial fibrillation; VPCs, ventricular premature complexes; PVTachy, paroxysmal ventricular tachycardia; 1°/2°, first degree/second degree; 3°, third degree; AVB, atrioventricular block; CHF, congestive heart failure; TBE, thromboembolism.

exceptions, such as tachyarrhythmias, may accompany ventricular pre-excitation[14–16] or atrioventricular conduction abnormalities associated with atrial or ventricular septal defects.[5, 13]

ACQUIRED HEART DISEASES

CARDIOMYOPATHIES

Myocardial diseases represent the most common category of feline heart disease.[4, 5, 10, 17] The incidence of associated arrhythmias recorded at two large veterinary institutions is illustrated in Table 19–1 and Figure 19–1. From a survey at Angell Memorial Animal Hospital in Boston (Table 19–1), arrhythmias were most commonly recorded in the presence of congestive heart failure or thromboembolism. Ventricular extrasystoles were most prevalent, especially with decompensated cardiomyopathy. Supraventricular extrasystoles were the second most commonly recorded arrhythmia. From a survey of feline hypertrophic cardiomyopathy (HCM) and myocardial failure at the Animal Medical Center in New York[17a] (Fig. 19–1), ventricular extrasystoles were recorded in approximately one third of affected animals. Supraventricular premature complexes were recorded in 15 to 25 percent of cats from both groups. First-degree AV block was observed in about half the cats from one population with myocardial failure, but in only one cat from a study of HCM. In contrast, severe left axis deviation compatible with left anterior fascicular block was recorded in 11 percent of HCM cats but in none of the cats with myocardial failure.

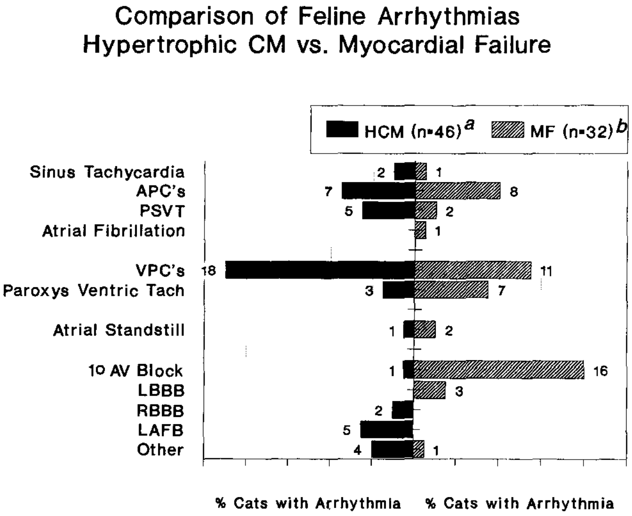


FIGURE 19–1

Graph contrasting arrhythmias recorded from two populations of cats at The Animal Medical Center with idiopathic hypertrophic cardiomyopathy and myocardial failure. APCs = atrial premature complexes; PSVT = paroxysmal supraventricular tachycardia; VPCs = ventricular premature complexes; LBBB = left bundle branch block; RBBB = right bundle branch block; LAFB = left anterior fascicular block. ([a]Data from Fox PR, Liu SK, Maron BJ: Echocardiographic identification of spontaneously occurring feline hypertrophic cardiomyopathy: An animal model of human disease. Circulation 92:2645, 1995; [b]data from Fox PR, unpublished, 1995.)

HYPERTHYROIDISM

A wide variety of ECG changes have been reported with feline hyperthyroidism[1, 2, 6, 8, 18–20] (chapter 34). Arrhythmias are especially prevalent when hyperthyroidism is chronic, associated with severe serum thyroid hormone elevation, cardiomegaly, and heart failure. Classic ECG changes include sinus tachycardia (heart rate > 240/min), increased R wave amplitude (> 0.9 mV, lead II), atrial and ventricular arrhythmias, prolonged QRS duration, shortened Q-T interval, and intraventricular conduction disturbances. With increasing clinical awareness and earlier detection of hyperthyroidism, this condition is now generally diagnosed sooner than in those patients reported in earlier literature. Accordingly, the incidence and severity of ECG abnormalities are reduced.

SYSTEMIC AND METABOLIC DISEASES

Atrial myocardium and the sinoatrial node are very sensitive to effects of elevated potassium.[21] Severe hyperkalemia causes atrial standstill and a sino-ventricular rhythm (see Figure 33–7) that may be complicated by acidosis and other electrolyte alterations. Hyperkalemia is a common extracardiac cause of feline arrhythmias. This is most prevalent with urethral obstruction from feline lower urinary tract disease, whereas acute renal failure and hypoadrenocorticism are less frequent etiologies. Reperfusion following arterial thromboembolism may represent a more common cause of hyperkalemia than previously realized.[20a]

CONSEQUENCES OF ARRHYTHMIAS

Arrhythmias are clinically deleterious when they cause hemodynamic impairment or degenerate into electrically unstable forms.[21] Many arrhythmias cause no perceptible clinical signs. Others result in lethargy, episodic weakness, syncope, or shock; contribute to or exacerbate congestive heart failure; or cause sudden death. Coexisting conditions such as acquired or congenital heart disease or systemic disorders may heighten or exacerbate their adverse hemodynamic effect and contribute to morbidity and mortality.

Certain physiologic variables such as cardiac preload and afterload and inotropic, and lusitropic status will influence the clinical effect that an arrhythmia might produce (chapters 3, 11). Since cardiac output is the product of heart rate and stroke volume, excessively slow (< 100/min) or rapid (> 280/min) heart rates can reduce cardiac output, especially when underlying myocardial disease is present. Asynergy resulting from uncoordinated atrioventricular activation and contraction may affect ventricular filling, decrease cardiac preload, and ultimately reduce cardiac output. Most sustained tachyarrhythmias increase cardiac work and associated myocardial oxygen demand in the face of reduced coronary perfusion. This results in myocardial ischemia, which can lead to further reduction in myocardial contractility—the potentially reversible "cardiomyopathy" of tachycardia.[22] Asynchrony between atrial and ventricular filling and contraction reduces cardiac performance. Loss of atrial contribution to filling, as caused by atrial fibrillation, may significantly reduce cardiac output.[23] The frequency and duration of arrhythmia are additional factors affecting cardiac function and clinical signs. For example, very brief paroxysms of tachycardia or bradycardia (i.e., 2 to 5 sec) may not result in clinical signs, whereas longer or sustained arrhythmia may cause weakness, syncope, or heart failure.

GOALS OF ANTIARRHYTHMIC THERAPY

When pharmacologic intervention is warranted, the goals of therapy should be to (1) terminate or suppress symptomatic tachycardia or bradycardia, (2) provide prophylaxis against recurrence, and (3) reduce arrhythmia-associated morbidity and mortality (see also chapter 18). Unfortunately, few data exist regarding optimal antiarrhythmic treatment.

APPROACH TO THE CAT WITH ARRHYTHMIAS

Arrhythmia detection is hampered by some of the unique qualities of felines and their cardiovascular diseases. Firstly, compared with dogs, cats display fewer classic recognizable signs of heart failure and do not cough with pulmonary edema. Secondly, their seclusive nature inhibits recognition of exercise intolerance. Thirdly, syncope and weight loss, common with canine heart failure, are uncommon with feline cardiac disorders.

Heart murmurs that accompany feline myocardial diseases are usually soft and are easily missed during a hastily conducted physical examination. During auscultation, rapid feline heart rates may obscure gallop rhythms, and they make diagnosis of tachycardias and extrasystoles more difficult than in dogs, which have slower heart rates.

HISTORY AND PHYSICAL EXAMINATION

These are often overlooked and abbreviated, but when conducted well, they provide important clues

to the presence of cardiac disease (chapter 5). The incidence of serious rhythm disturbances increases as the severity of heart failure worsens (see Table 19–1). Syncope may be related to advanced atrioventricular block or tachyarrhythmia. Intermittent claudication or acute paresis can result from arterial thromboembolism. For reasons that are not clear, many cats vomit during congestive heart failure. Physical examination may disclose evidence of heart disease, including tachypnea, jugular venous pulses, weak or irregular femoral arterial pulses that vary in strength, cyanotic mucous membrane color, ascites and hepatomegaly, and hypothermia. Auscultatory abnormalities include lung crackles, muffled heart and lung sounds, heart murmur, gallop rhythm, and irregular, slow, or rapid heart rate. Due to the rapid feline heart rate, extrasystoles are usually heard as pauses, not "extra" beats. In the absence of clinical signs, evidence of a heart murmur, gallop rhythm, or an irregular heart rate provides sufficient justification for an electrocardiogram and additional diagnostic tests.

MINIMUM DATA BASE

This is modified by the signalment, history, and physical examination. It generally includes an electrocardiogram, thoracic radiographs, echocardiogram, blood pressure measurement, and serum thyroxine (T_4) assay. Ancillary tests such as a biochemical profile, urinalysis, hemogram, fluid cytology, and heartworm test may be beneficial.

ELECTROCARDIOGRAPHY

In eupneic cats, the ECG is often recorded with the cat restrained in right lateral recumbency (chapter 6). In fractious animals, a nylon muzzle or an Elizabethan collar may be useful, although chemical restraint is sometimes necessary. Intravenous ketamine hydrochloride (1 to 2 mg/kg) provides good short-term immobilization but is arrhythmogenic, especially in the presence of heart failure or thyrotoxicosis. In dyspneic cats, stress must be avoided, and ECG recordings can be made with the cat standing or in sternal recumbency.

Because of the transient nature of many arrhythmias, a single rhythm strip or twelve-lead ECG recording may not disclose the abnormality. Chances for detection are increased in proportion to the frequency and duration of recordings. Sometimes, allowing the cat to stand up with the ECG leads remaining attached provokes some arrhythmias by transiently increasing stress. When not successful, hospitalizing the cat for frequent rhythm strip recordings may increase diagnostic opportunities. Alternatively, ECG telemetry is generally well tolerated, or 24-hour Holter recordings may be beneficial.[20a]

STEPS TO ASSIST ARRHYTHMIA DIAGNOSIS

Diagnosis of some arrhythmias can be enhanced by certain steps, actions, and observations. These are outlined next.

VAGAL MANEUVERS

Vagal stimulation allows for dynamic modulation of heart rate and AV nodal conduction. Parasympathetic discharge releases acetylcholine, which slows the sinoatrial (SA) nodal discharge rate and prolongs AV nodal conduction time and refractoriness.[24] In some arrhythmias caused by the re-entry mechanism, increased vagal tone may alter re-entry pathway refractoriness and terminate the supraventricular tachycardia. Sinus tachycardia slows gradually during vagal stimulation and returns to the previous rate when the maneuver is discontinued. Vagus-induced slowing of AV conduction may expose atrial activity (P waves) by "unmasking" previously unidentifiable P waves from preceding T waves by transiently slowing the heart rate. Vagal maneuvers performed during simultaneous ECG recording include carotid sinus massage (preferred method) and eyeball pressure (rarely effective) (see Fig. 18–7). Facial immersion in cold water (dive reflex) and gagging are additional maneuvers used in humans. Vagal maneuvers should be avoided when advanced AV block or significant bradyarrhythmias are detected.

PHYSICAL EXAMINATION FINDINGS: AUSCULTATION, PALPATION, AND BLOOD PRESSURE

Elevations of jugular venous pressure can reflect increased right atrial pressure in right-sided CHF. Abnormal jugular venous pulsations and associated giant (cannon) *a* waves may be noted with AV dissociation and complete AV block when the right atrium (RA) contracts against a closed tricuspid valve. During regular supraventricular tachycardia, a consistent arterial pulse, blood pressure, and first heart sound are usually detected. In contrast, tachyarrhythmias causing variable AV conduction (e.g., atrial fibrillation, atrial flutter) cause inconstant arterial pulses, changing arterial blood pressure, and differing loudness of the first heart sound.

TIPS AND CONSIDERATIONS FOR ECG EVALUATION

ELIMINATE ARTIFACT. One of the greatest causes of ECG misinterpretation is artifact in the recorded ECG. By positioning the lead wires so they do not overlap,

cross, or lie over the cat, movement of these leads and associated motion artifact are eliminated. Restraint techniques that minimize movement but do not stress the cat should always be selected.

USE CALIPERS, ECG RULERS, AND MAGNIFICATION FOR ECG ANALYSIS. The rapid feline heart rate and low-voltage ECG complexes may necessitate careful scrutiny of P-QRS-T intervals and measurements. Often, these cannot be adequately assessed by unaided visual inspection.

METICULOUSLY EVALUATE THE ECG. The entire ECG, including all leads, should be assessed. One should compare morphologic features recorded during the arrhythmia with similar wave forms recorded during sinus rhythm in the same leads. Careful scrutiny of QRS complexes and T waves must be made for "hidden" P waves.

STRESS ELECTROCARDIOGRAPHY. Certain arrhythmias may be provoked during stress or exercise. Care must be taken, and this maneuver should be avoided, if congestive heart failure is present.

USE ADDITIONAL DIAGNOSTIC ECG LEADS. In addition to a lead II rhythm strip, a 10-lead ECG that includes precordial chest leads should be recorded.[11] These may contain morphologic clues to P-QRS-T complex configuration.

ARRHYTHMIAS: DIAGNOSIS AND THERAPY

SINUS RHYTHMS

NORMAL SINUS RHYTHM. In the healthy cat, normal sinus rhythm represents the basic underlying rhythm (in comparison, sinus arrhythmia is the most common canine rhythm). ECG characteristics include (1) regularly occurring P waves with less than 10 percent variation between P and P intervals, (2) a fixed relationship between P waves and subsequent QRS-T complexes, and (3) a rate of 140 to 220/minute.

SINUS TACHYCARDIA. This is characterized by heart rates greater than 220/minute in which the identical P-QRS-T relationships are maintained (see Figure 6–32).

SINUS BRADYCARDIA. When the dominant pacemaker originates in the SA node but discharges at less than 140 beats/minute (see Figure 6–34), sinus bradycardia is present. The standard P-QRS-T relationship is maintained.

SINUS NODAL DISTURBANCES

ECG CHARACTERISTICS. Dysfunction of the sinoatrial (SA) node can reduce the pacemaker discharge rate, resulting in mild slowing to complete absence of SA node activity. The latter causes lack of atrial activation for one or more beats during the expected sinus rhythm and results in a pause recorded on the ECG. This is called *sinus arrest, sinoatrial arrest,* or *sinus pause.* It is characterized by a P-P interval that "straddles" the pause in the rhythm, and which does not equal a multiple of the basic P-P interval. *Sinoatrial block* or *sinoatrial exit block* occurs in the presence of "normal" sinus node function but with periodic failure of impulse conduction from the SA node to the surrounding atrial tissue. Like sinus arrest, sinoatrial block causes a pause in the rhythm owing to the absence of a normally expected P wave. In contrast, however, the duration of the pause is an exact multiple of the basic P-P interval. Differentiating sinus arrest from sinoatrial block when sinus arrhythmia is present is difficult without direct sinus node recordings, an invasive and clinically unnecessary procedure.[25]

ETIOLOGIES. Associated causes are varied and range from systemic and metabolic disorders to organic heart disease. Causes of vagotonia include brachycephalic breeds, upper respiratory infection or airway obstruction, anterior mediastinal masses, and surgical manipulations.

CLINICAL FEATURES. Only rarely are clinical signs attributable to sinus node dysfunction. Occasionally, lethargy, anorexia, or episodic weakness may be present. In most circumstances the condition may go unrecognized until the cat is presented for a routine visit or for some unrelated complaint.

THERAPY. Treatment of sinus node dysfunction should be directed at the underlying cause. When it results from cardioactive drugs, lower dosages, alternative agents, or drug withdrawal should be initiated. When secondary to general anesthesia, reduction of anesthetic depth is warranted; if unsuccessful, a parasympatholytic drug such as atropine sulfate or glycopyrrolate may be administered. Sinus bradycardia resulting from surgical manipulation of cervical or cranial mediastinal structures can usually be counteracted by more gentle tissue handling or use of parasympatholytic agents. When sinus node dysfunction occurs due to organic heart disease, the response to drug therapy is frequently ineffective and unpredictable.

SUPRAVENTRICULAR ARRHYTHMIAS

ECG CHARACTERISTICS. The term "supraventricular" implies that the site of abnormal discharge originates in the atria proximal to the bundle branches, and it is used to describe both atrial and AV junctional ectopia. These arrhythmias generally have in common a QRS complex that is identical, or almost so, to the normal sinus-generated QRS complex, unless aberrant ventricular conduction is present, as occurs with atrial fibrillation.[21]

Nomenclature varies with respect to classification of supraventricular arrhythmias (chapter 6), and some controversy exists regarding terminology. Tachycardias are sometimes differentiated as to whether the QRS complexes are narrow (< 0.045 sec)—i.e., *narrow QRS tachycardia,* or wide—i.e., *wide QRS tachycardia. Supraventricular* is a broad term that encompasses arrhythmias originating in the atria or AV node. For the sake of clarity, a set of descriptive titles has been proposed for supraventricular arrhythmias (see Table 6–5).

ETIOLOGIES. Supraventricular arrhythmias most commonly result from conditions causing significant atrial enlargement.[1,2] Hypertrophic and restrictive cardiomyopathies are most commonly responsible. Congenital heart diseases associated with severe volume overload and extracardiac disorders are occasionally causative. Congestive heart failure seems to enhance the incidence. Isolated supraventricular extrasystoles are common in advanced heart disease, whereas tachyarrhythmias are less frequently detected. The latter may result from or contribute to the onset of cardiac decompensation.

CLINICAL FEATURES. Rapid ventricular rates may cause hemodynamic impairment manifested as lethargy, hypotension, heart failure, or collapse. This is somewhat dependent upon underlying cardiac function but is more likely to occur at ventricular rates greater than 250 to 270/minute. Syncope is occasionally associated with rapid ventricular rates, especially with hypertrophic cardiomyopathy.

ATRIAL EXTRASYSTOLES (Fig. 19–2)

These premature complexes occur earlier than expected with QRS-T conformation identical to or very similar to the normal QRS morphology. Due to early depolarization of the sinus node by the supraventricular premature discharge, the normal sinus pacemaker is reset causing a *noncompensatory pause* (i.e., the two P-P intervals encompassing the premature complex are shorter than the interval measured from two normal, expected P-P intervals). The term "supraventricular premature complex" is a broader term that includes extrasystoles that occur in the atria and AV node. They may occur singly, as two in succession (a pair or couplet), or as three or more in a series (a run).

ATRIAL TACHYCARDIA (Fig. 19–3)

This tachyarrhythmia is present when four or more supraventricular premature complexes occur in succession, usually associated with a ventricular rate of 270 to 400/minute. It may occur in short bursts or for prolonged periods. The term "supraventricular tachycardia" is sometimes applied as a broader term to encompass arrhythmias originating in the AV node. Vagal maneuvers may abolish some tachyarrhythmias or unveil P waves.

ATRIAL FLUTTER

Atrial flutter is a rare, generally transient tachyarrhythmia characterized by (1) a rapid atrial rate whose P waves may display a saw-toothed morphology *(flutter waves),* and (2) variable atrioventricular conduction resulting in recognizable flutter (P) waves with an irregular ventricular rhythm. Sustained supraventricu-

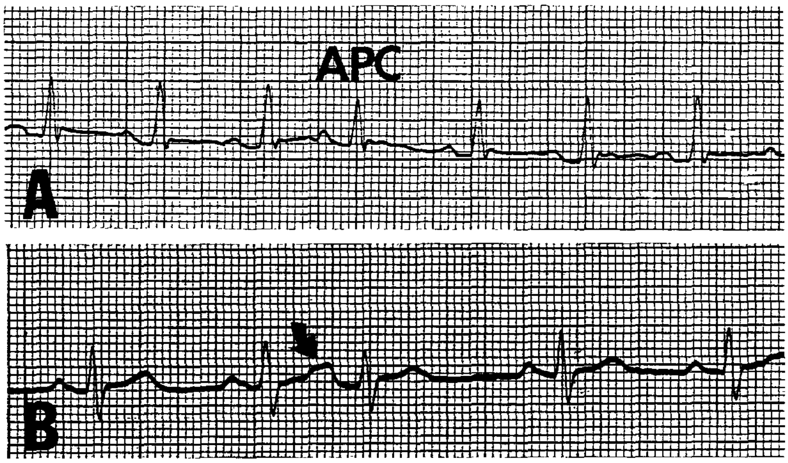


FIGURE 19–2

Atrial premature complexes (APCs) recorded from two different cats with hypertrophic cardiomyopathy (lead II). (A) Premature P′ wave morphology is slightly different from the preceding normal P waves. (B) Premature P′ wave is inscribed during the end of the preceding T wave, causing the latter to be enlarged and notched (arrow). The QRS complex is wider than normal, suggesting LV enlargement. In each cat, a noncompensatory pause follows the APC. The QRS morphology of the APCs here are slightly different from the normal complexes, suggesting aberrant conduction. Paper speed, 50 mm/sec; 1 cm = 1 mV.

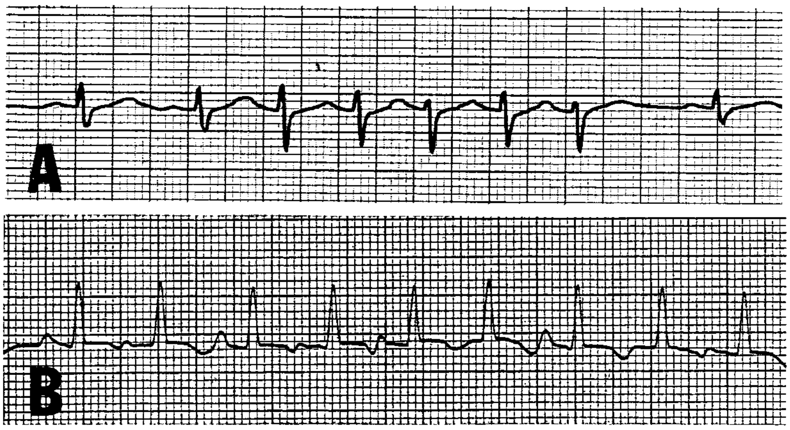


FIGURE 19–3

Paroxysmal supraventricular tachycardia recorded from two cats (lead II) with myocardial disease and severe left atrial enlargement. (A) A paroxysm of 5 extrasystoles follows the second complex from the left. P′ waves are not readily identifiable. (B) APCs and paroxysmal supraventricular tachycardia are recorded. The premature P′ waves are identifiable and vary in morphology (compare with the normal P waves), suggesting atrial tachycardia. Paper speed, 50 mm/sec; 1 cm = 1 mV.

lar tachycardia may be difficult to differentiate from atrial flutter with a regular, fixed conduction pattern (i.e., 1:1 or 2:1 conduction). Vagal maneuvers may assist in diagnosis.

ATRIAL FIBRILLATION (Fig. 19–4)

This serious arrhythmia is usually associated with cardiomyopathy in which significant atrial enlargement is present. It is characterized by replacement of normal P waves with irregular and chaotic baseline fluctuations *(fibrillation waves).* Due to varying AV nodal and ventricular conduction, QRS complex morphology is often nonuniform. The ventricular rate may vary from 150 to 320/minute.

PERSISTENT ATRIAL STANDSTILL

This uncommon arrhythmia is usually associated with severe, long-standing heart disease. There is total absence of P waves, bradycardia, and an escape rhythm of supraventricular or ventricular morphology.[26]

THERAPY OF SUPRAVENTRICULAR ARRHYTHMIAS

Isolated *supraventricular extrasystoles* are not suppressed *per se.* They are present in many cats with compensated myocardial disease and occasionally herald cardiac decompensation. Sustained or symptomatic supraventricular tachycardias are usually treated. If the diagnosis is uncertain with *wide QRS complex tachycardia,* initial vagal maneuvers may help distinguish supraventricular tachyarrhythmias with aberrant ventricular conduction from ventricular tachycardia by slowing the heart rate and unmasking hidden P waves, or by terminating the tachycardia.

Vagal maneuvers may temporarily terminate certain supraventricular tachycardias. Sinus tachycardia may be temporarily slowed but not abolished. Ventricular

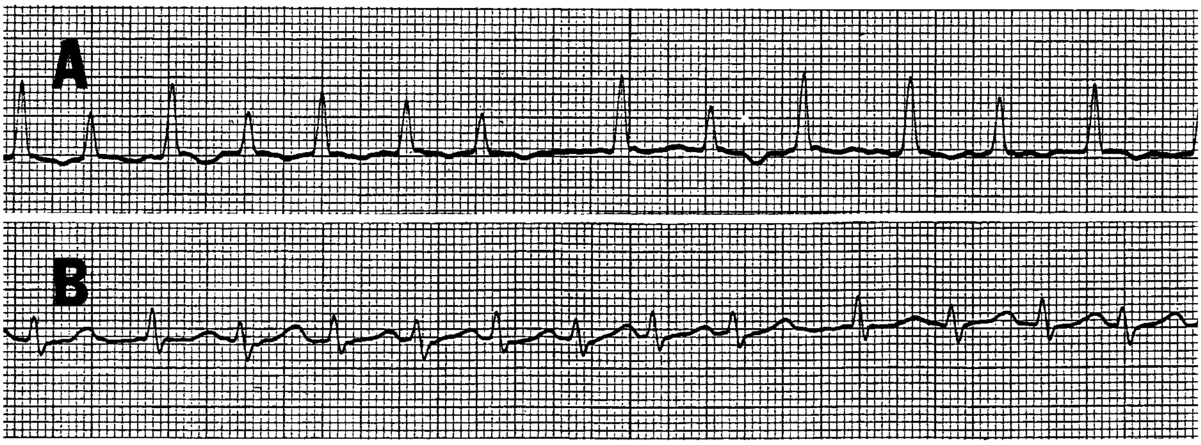


FIGURE 19–4

Atrial fibrillation recorded from two cats (lead II) with severe left atrial enlargement associated with hypertrophic (A) and restrictive (B) cardiomyopathy. Both ECG recordings are characterized by an irregularly irregular tachycardia with absence of P waves. (A) The QRS complexes vary due to aberrant ventricular conduction (average heart rate, 240/min). (B) With a rapid tachycardia (heart rate, 200 to 300/min), the R-R interval irregularities are generally less noticeable. Paper speed, 50 mm/sec; 1 cm = 1 mV.

tachyarrhythmias are nonresponsive to vagal maneuvers.

Digoxin is usually administered for persistent supraventricular tachyarrhythmias. Oral digoxin, 0.031 mg (i.e., one fourth of a 0.125-mg tablet) daily or every other day for an average-sized cat[4] is usually combined with a β-adrenergic blocker or a calcium channel blocker. Doses are titrated to effect in order to reduce the ventricular rate or abolish the tachyarrhythmia. Due to renal elimination, kidney failure will reduce excretion and increase serum digoxin concentration.[27, 28] Steady state digoxin blood levels are usually reached after approximately 7 to 10 days. Anorexia and depression are early signs of toxicity. ECG evidence of digoxin toxicosis generally includes first-degree AV block, although clinical toxicity may precede ECG changes; severe toxicity may cause advanced AV block, bradycardia, and arrhythmias.

Calcium channel blockers slow AV nodal conduction and have been used with digoxin, with beta-adrenergic receptor blockers, or as monotherapy. Diltiazem has been the most widely used agent and is usually dosed at 7.5 mg bid to tid orally. As monotherapy, however, it rarely reduces the ventricular rate with atrial fibrillation.

Chronic management for tachyarrhythmias should be planned with complete knowledge of the underlying heart disease and general health status. Treatment must be tailored to meet individual patient needs. Control of the heart failure may itself be effective in terminating or controlling tachyarrhythmias.

VENTRICULAR PRE-EXCITATION

(Fig. 19–5)

Ventricular pre-excitation syndrome occurs when an impulse bypasses the AV node and activates the whole or some portion of the atrium or ventricle earlier than

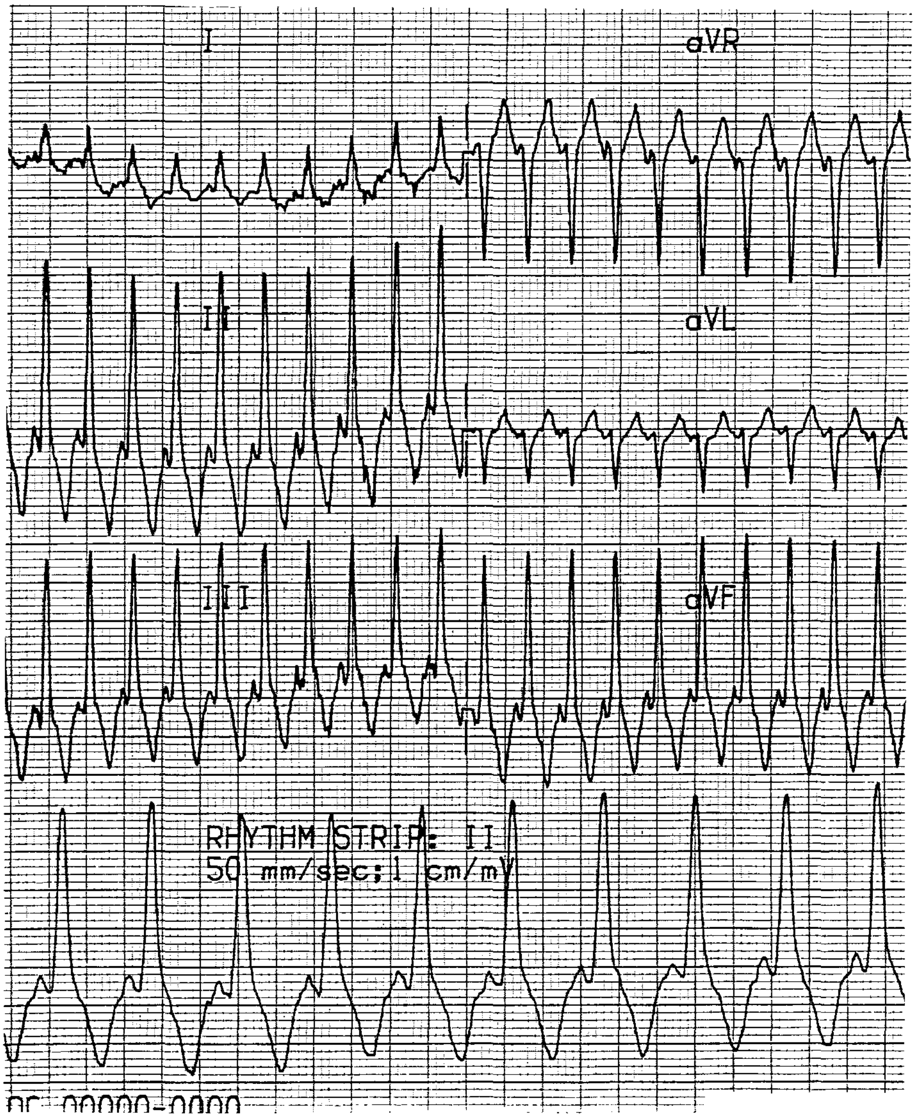


FIGURE 19–5

Ventricular pre-excitation recorded from a clinically normal cat. The PR interval is very short because the sinus-originated impulse is conducted through an accessory pathway, bypassing the AV node and its associated conduction delay. The QRS complexes are wide and tall. Slurring of the R wave upstroke is difficult to see but is suggested in lead I. Paper speed 25 mm/sec for all leads except lead II rhythm strip (50 mm/sec); 1 cm = 1 mV.

would be anticipated by passage of the impulse by way of the normal conduction pathways. A number of aberrant connections responsible for this syndrome have been reported.[16] In the Wolff-Parkinson-White (WPW) syndrome, abnormal accessory atrioventricular pathways (Kent's bundles) connect atria and ventricles.[29, 30] Other abnormal AV pathways can partially or wholly short-circuit the AV node, resulting in accelerated AV conduction. These include atrio-His or atriofascicular tracts[31] and Mahaim's fibers, which pass directly from the A-V node to the ventricle. Both the atrioventricular and atriofascicular varieties have been reported in the cat.[1, 14–16, 32]

ECG CHARACTERISTICS. Ventricular pre-excitation may produce different ECG changes depending on the location and arrangement of accessory AV pathways. Common findings include (1) shortened P-R interval, usually less than 40 msec; frequently, the PR segment is totally missing or the P wave is transcribed at the base of the R wave upstroke; (2) the QRS configuration can vary based upon position of abnormal AV pathway(s) and the relative rates of AV conduction between abnormal and normal AV conduction pathways. The QRS interval is normal in the atriofascicular form but is prolonged in the other forms of pre-excitation. When the QRS interval is prolonged, some leads may show a slowly rising, slurred QRS upstroke, known as a *delta wave*; (3) intermittent or sustained tachyarrhythmias, termed AV re-entrant, circus movement, or reciprocating tachycardia, may be present. Orthodromic AV tachycardia is the most common cause of reciprocating tachycardia. It consists of a circuit initiated by normal AV conduction through the AV node, His' bundle, and the bundle branches, with subsequent retrograde ventriculoatrial (VA) conduction back to the atria by the abnormal AV pathway.

CLINICAL FEATURES. Most affected cats have no clinical signs. Occasionally, paroxysmal or sustained tachycardia may occur with associated lethargy, anorexia, episodic weakness, or collapse. The ECG waveforms may appear as wide-complex tachycardia and thus resemble ventricular tachycardia, making correct diagnosis challenging.

THERAPY OF VENTRICULAR PRE-EXCITATION

Unless clinical signs or significant tachyarrhythmias are present, therapy is not advocated. Cats with symptomatic tachyarrhythmias should receive an initial vagal maneuver. If ineffective, judicious intravenous administration of diltiazem or verapamil may be attempted and can be coupled with repeated vagal maneuvers. If still ineffective, then antiarrhythmic agents that depress conduction in abnormal pathways can be administered. Adenosine, digoxin, β-adrenergic blockers, and calcium channel blockers prolong AV nodal conduction time and refractoriness. Neither β-blockers nor calcium channel blockers directly affect conduction through accessory pathways. However, digitalis can shorten refractoriness in accessory pathways and deleteriously speed ventricular conduction; therefore, it should not be used. Drugs that prolong refractoriness in accessory pathways (e.g., quinidine, procainamide) have been advocated in humans but have not been well-studied in cats. We have occasionally administered oral procainamide and quinidine in selected cases. Catheter or surgical ablation may be pursued at highly specialized centers if oral drug therapy is ineffective.[16]

ATRIOVENTRICULAR NODE DYSFUNCTION (Fig. 19–6)

Normal atrial impulses travel by specific internodal tracts to the AV node, where impulse conduction is slowed before progressing through the bundle of His to the bundle branches and Purkinje system. The AV node is subdivided into the AN (atrionodal), the N (nodal), and the NH (nodal-His bundle) regions. Progressive slowing of conduction[33] begins in the AN region and reaches a maximum in the N region. Then, conduction velocity gradually increases in the NH region as the His bundle is approached.[34] This slowed conduction permits optimal timing for atrial depolarization and contraction, thereby obtaining maximal preload allowing atrial contribution to ventricular filling, and somewhat inhibits conduction of rapid, atrial arrhythmias to the ventricles. Atrioventricular nodal abnormalities cause conduction impediment, called heart block. These may be characterized as incomplete (1° and 2°) and complete (3°) AV block.

ECG CHARACTERISTICS. Atrioventricular block causes delay of impulse conduction through the AV node or interruption of electrical impulses from the atria to the ventricles. Depending on lesion severity, the block may be incomplete (1° or 2°) or complete (3°).

FIRST-DEGREE AV BLOCK (Fig. 19–6*A*). Atrioventricular conduction is slowed as evidenced by PR interval prolongation (>0.09 sec), but all impulses are conducted though the AV node into the ventricles. A consistent 1:1 relationship is present between P waves and QRS-T complexes.

SECOND-DEGREE AV BLOCK (Fig. 19–6*B, C*; see also Figure 6–20). There is failure of one or more atrial impulses to conduct to the ventricles. Two forms of 2° AV block occur:

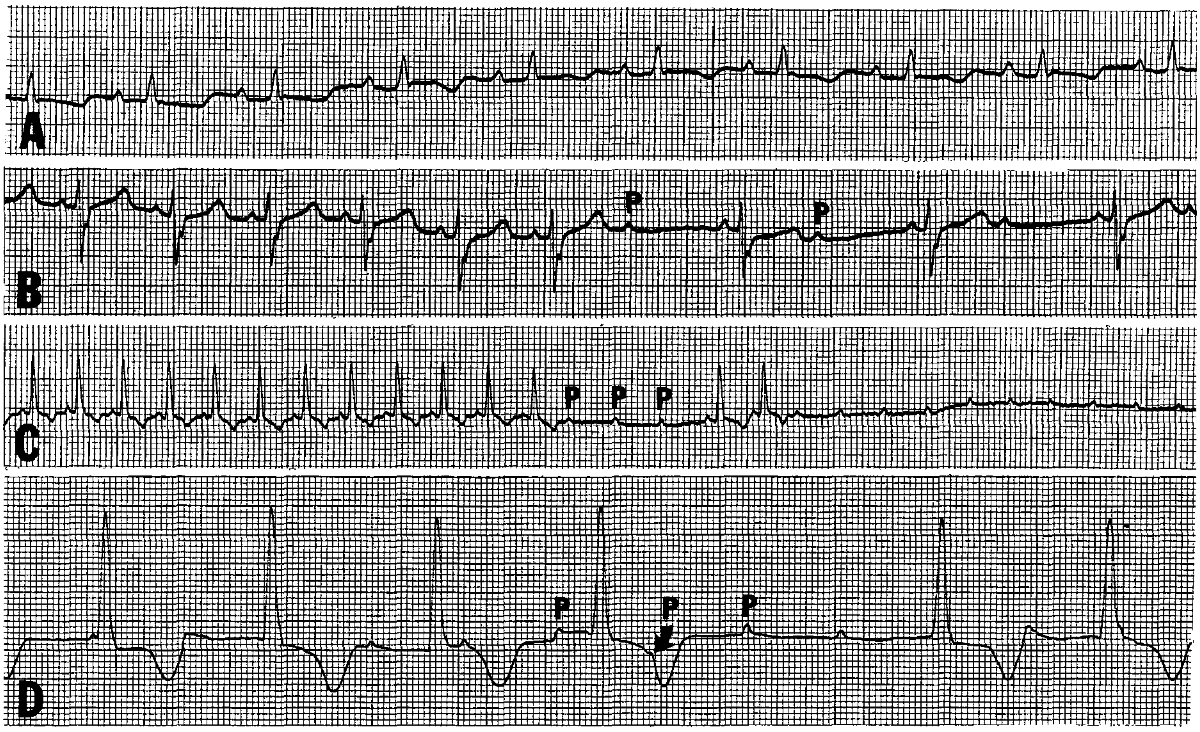


FIGURE 19–6

Examples of different forms of heart block from four cats (lead II). (A) First-degree (1°) AV block in a cat with hypertrophic cardiomyopathy. The PR interval measures 110 msec, which is prolonged (normal is ≤ 90 msec). Heart rate is approximately 135/min. These changes were due to β-adrenergic blocker (propranolol) therapy. (B) Second-degree (2°) AV block (Mobitz II) in a cat with right bundle branch block. There is intermittent block of atrioventricular conduction as evidenced by P waves (P) without QRS complexes. The PR intervals are constant. (C) Advanced (high-grade) 2° AV block in a cat with syncope. (D) Complete (3°) AV block recorded from a cat with acute lethargy. There is no relationship between P waves and QRS-T complexes. A ventricular escape rhythm (approximately 100/min) is present.

(1) *Mobitz's Type I (Wenckebach's phenomenon)* 2° AV block is characterized by progressive PR interval prolongation until a beat is "dropped" (i.e., a P wave is present without an associated QRS-T complex) (see Figure 6–20).

(2) *Mobitz's Type II 2° AV block* shows a fixed P-R interval in conducted impulses with occasional failure of AV conduction (i.e., P wave without associated QRS-T complex) (Fig. 19–6*B*).

In *advanced 2° AV block,* two or more successive P waves are blocked (Fig. 19–6*C*). For example, in 3:1 AV block, three P waves occur to each QRS-T complex. The P-R interval of conducted beats is usually constant but tends to be prolonged.

THIRD-DEGREE AV BLOCK (Fig. 19–6*D*) represents total disruption of atrioventricular conduction. The atria and the ventricle beat independently of one another at their own intrinsic rates. The ventricular rate is usually substantially slower than the atrial rate and usually ranges from 60 to 100/minute. Its QRS-T configuration varies and is dependent upon the origin of the ventricular pacemaker tissue.[35–37]

ETIOLOGIES. A variety of primary cardiac and extracardiac factors can be responsible (see Table 19–1).[2, 3, 12, 35] First-degree AV block and Mobitz's Type I second-degree AV block may result from anesthetic agents, β-adrenergic receptor blockers, calcium channel blockers (high doses), and digitalis glycosides. First-degree AV block is the most common ECG abnormality recorded in cats with idiopathic myocardial failure. The remaining forms of 2° and 3° AV block more frequently result from organic heart disease, especially myocardial disorders.

Clinically significant bradyarrhythmias are rare. When they occur, it is usually with organic heart disease (cardiomyopathy). Associated pathology includes myocardial ischemia, infarction, fibrosis, or conduction tissue infiltration. These changes cause sinus node dysfunction or disruption of the atrioventricular conduction pathways. In other cases, bradyarrhythmias result from severe systemic or metabolic illness.

CLINICAL FEATURES. Advanced 2° and 3° AV block may be associated with lethargy, episodic weakness, or syncope. In some cats with significant pre-existing cardiac disease, the onset of advanced AV block may reduce

cardiac output and precipitate clinical signs or exacerbate heart failure. Advanced 2° AV block tends to alternate with 3° AV block,[36, 37] and both tend to cause clinical signs over time.

THERAPY OF ATRIOVENTRICULAR BLOCK

Iatrogenic AV block caused by digoxin, β-adrenergic blockers, or calcium channel blockers may require dosage reduction or drug withdrawal. When hemodynamically significant AV block occurs under heavy sedation or general anesthesia, anesthetic reduction or narcotic antagonist reversal is indicated. Parasympatholytic agents may be used in these circumstances if anesthetic reduction is unsuccessful. Short-term management of symptomatic AV block can be attempted with intravenous constant rate infusion of a sympathomimetic agent (isoproterenol, 0.02 to 0.04 μg/kg/min, or dopamine, 2–7 μg/kg/min [beware of a pressor effect at higher doses]) or parasympatholytic drug (atropine sulfate, 0.02 to 0.04 mg/kg; glycopyrrolate, 0.005 to 0.01 mg/kg), but these agents rarely enhance AV conduction or reverse clinical signs. Temporary transvenous cardiac pacing may provide hemodynamic stabilization. Permanent pacemaker therapy is the only dependable treatment for the long-term management of symptomatic AV block (chapter 20).[36–38] When AV conduction abnormalities result from organic heart disease, neither the underlying disorder nor the AV block is usually reversible. Exceptions include secondary myocardial disorders related to thyrotoxicosis (chapter 34), taurine deficiency (chapters 28, 32), and other noncardiac conditions (chapter 33). First-degree AV block and uncomplicated second-degree AV block do not require specific treatment as they cause no hemodynamic instability. Periodic ECG monitoring is advised.

VENTRICULAR ARRHYTHMIAS

(Figs. 19–7, 19–8, 19–9)

Ventricular extrasystoles and tachycardias are the most common feline arrhythmias (Fig. 19–1; see Table 19–1).[1, 2] They originate distal to the bundle of His in either specialized conduction tissues, ventricular myocardial fibers, or both. Sustained or multifocal ventricular tachycardia possesses a great potential for electrical instability, or it may deteriorate into hemodynamically unstable ventricular flutter (Fig. 19–9*A*) and fibrillation (Fig. 19–9*B*).

ETIOLOGIES. Both extracardiac and primary cardiac disorders cause ventricular extrasystoles. Primary cardiomyopathies represent the most common form of associated heart diseases,[1, 2, 5, 10] whereas hyperthyroidism is the most frequently encountered form of secondary myocardial disease.[6–8] Ventricular ectopia is increased with congestive heart failure. Systemic thromboembolism,[1] infarction,[39] and aging are also associated with increased ectopia.

ECG CHARACTERISTICS. Ventricular extrasystoles (1) are premature beats; (2) have abnormal morphology whose ectopic QRS complex is wide (> 65 msec), bizarre in shape, with a large T wave oppositely directed from the major QRS deflection; (3) are dissociated from atrial activity (i.e., not conducted from a P wave); (4) may produce fusion beats (uncommonly in cats compared with dogs); and (5) usually produce a *compensatory pause* (Fig. 19–7*A*). They may occur singly, in pairs, or triplets (Fig. 19–7*B*, 19–8*A*). Four or more successive complexes constitute ventricular tachycardia (Fig. 19–8*B*, *C*). The QRS morphology can vary considerably according to site of origin, pathway of ventricular depolarization, and factors affecting the ventricular conduction system.

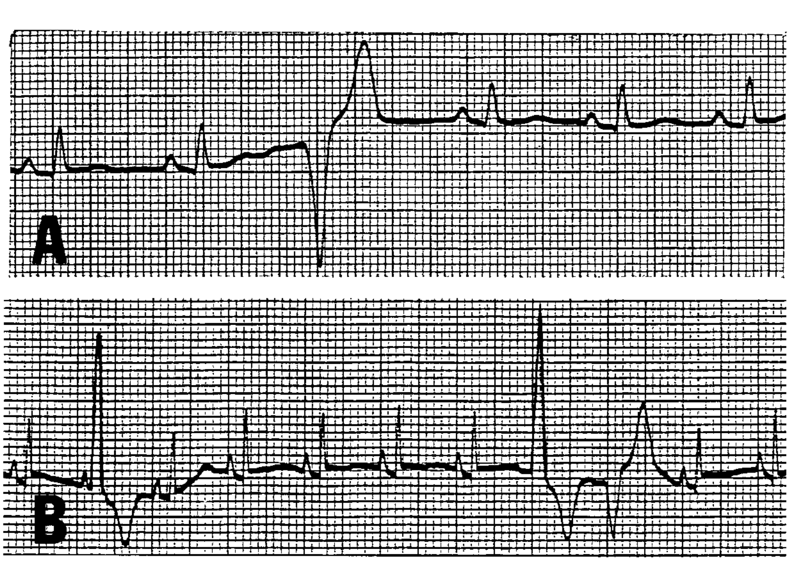


FIGURE 19–7

(A) Ventricular premature complex (VPC) recorded from a cat with restrictive cardiomyopathy. The VPC is an early, ectopic complex that is wide and bizarre and has a large T wave oriented opposite to the QRS deflection. A compensatory pause follows the VPC. Lead II; paper speed, 50 mm/sec; 1 cm = 1 mV. (B) Multifocal VPCs recorded from a hyperthyroid cat sedated with ketamine hydrochloride. Lead II; paper speed, 25 mm/sec; 1 cm = 1 mV.

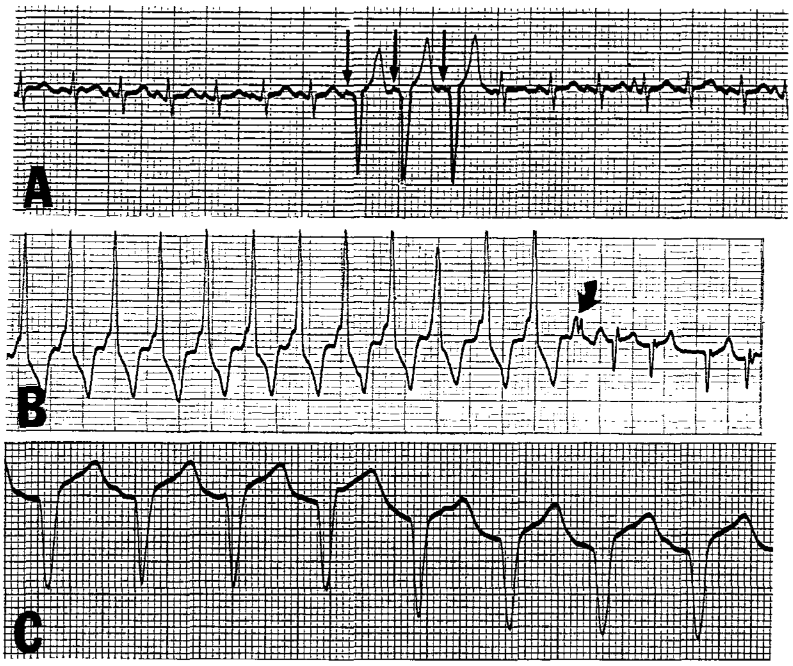


FIGURE 19–8

Ventricular tachycardia (VT) recorded from three cats with myocardial disease (lead II). (A) A short paroxysm recorded in an otherwise asymptomatic cat. Notice the P wave immediately preceding each VPC *(arrows)*. These sinus-initiated P waves are not conducted to the ventricles and have no relationship to the following QRS complexes. This atrioventricular dissociation is a characteristic of ventricular extrasystoles. Paper speed, 25 mm/sec; 1 cm = 1 mV. (B) Paroxysmal VT recorded from a cat with restrictive cardiomyopathy. The basic underlying arrhythmia is atrial fibrillation. A fusion complex *(arrow)* follows the paroxysm of VT. Paper speed, 25 mm/sec; 1 cm = 1 mV. (C) Sustained ventricular tachycardia recorded from a cat with dilated cardiomyopathy. The rhythm is regular with a ventricular heart rate of 200/min. QRS-T complexes are wide and bizarre. Some P waves can be observed partially "hidden" in the T waves, which confers a small notch or hump to the T wave (atrioventricular dissociation). Paper speed, 50 mm/sec; 1 cm = 1 mV.

CLINICAL FEATURES. Ventricular extrasystoles are frequently associated with underlying heart disease. Occasional ventricular premature contractions (VPCs) are commonly detected in older cats and are probably present in most animals with cardiomyopathy. Occasional extrasystoles cause no hemodynamic impairment or instability and require no treatment. However, they are generally deemed more important when multifocal or frequent in nature, although no studies have verified them as an increased risk factor in cats. When frequent VPCs accompany severe functional cardiac derangement, they contribute a negative hemodynamic effect, particularly when advanced myocardial failure is present. Ventricular tachycardia may exacerbate or worsen congestive heart failure and cause episodic weakness, collapse, or sudden death. It is generally treated regardless of cause.

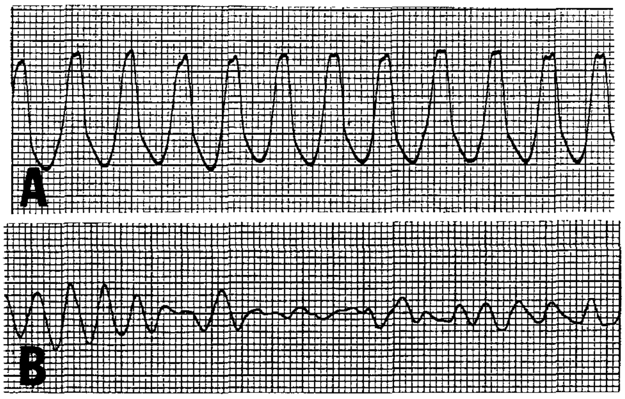


FIGURE 19–9

Hemodynamically and electrically unstable ventricular arrhythmias. (A) Ventricular flutter (>320/min) characterized by a continuous wave form, with inability to differentiate P-QRS-T waves. With onset of this arrhythmia the cat became moribund, hypotensive, and tachypneic. (B) Coarse ventricular fibrillation recorded during cardiac arrest. Oscillations are rapid and bizarre and lack any recognizable morphology. This arrhythmia is associated with total cessation of cardiac output and circulation. Paper speed, 50 mm/sec; 1 cm = 1 mV.

THERAPY OF VENTRICULAR ARRHYTHMIAS

For nonsymptomatic arrhythmias, thorough patient evaluation is advised to identify potentially reversible systemic or metabolic causes, and to assess underlying cardiac structure and function. Many cats with *occasional ventricular extrasystoles* or short-lived, paroxysmal tachycardia require no therapy. Treatment of asymptomatic cats is discouraged.

In contrast, suppressive pharmacologic therapy is indicated if the arrhythmia is (1) electrically unstable (e.g, multifocal VPCs; R on T phenomenon in which the R wave of the VPC falls in the vulnerable portion of the preceding T wave; or sustained ventricular tachycardia); or (2) hemodynamically unstable (i.e., causes lethargy, episodic weakness, hypotension, syncope, shock, or congestive heart failure). Suppression of all extrasystoles is usually not possible or necessary. Treatment of heart disease should be optimized according to the cat's individual requirements. Every attempt should be made to identify an underlying or precipitating etiology for the arrhythmia, such as hyperthyroidism, when heart failure is not causative. Close communication with the owner and regular patient follow-up are important.

VENTRICULAR TACHYCARDIA OR MULTIFOCAL VPCS. Initial emergency pharmacologic therapy for life-threatening,

sustained ventricular tachycardia consists of lidocaine HCl, 0.25 to 1 mg/kg IV over 5 minutes, or in a 1-mg bolus (up to a total of 4 mg for an average-sized cat).[2] Esmolol, 50 to 500 μg/kg IV bolus, or 50 to 200 μg/kg constant rate infusion, may be added or used as monotherapy. This ultra short-acting β-blocker may be titrated to effect. A high sympathetic tone may require larger doses. The effects on heart rate after singular IV boluses may be less than a minute, depending upon dose and prevailing autonomic tone. If lidocaine or esmolol are ineffective, striking the chest over the left precordium (thumpversion) may occasionally terminate the arrhythmia, presumably by mechanically inducing a premature ventricular extrasystole that interrupts the re-entrant pathway.

Chronic oral maintenance therapy, when required, is usually limited to β-adrenergic blockers such as propranolol (2.5 to 10 mg every 8 to 12 hours) or atenolol (6.25 to 12.5 mg every 12 to 24 hours). Occasionally, procainamide (3 to 5 mg/kg every 8 to 12 hours) is added when monotherapy is ineffective and arrhythmia suppression is deemed critical.

INTRAVENTRICULAR CONDUCTION ABNORMALITIES

Cats with blunt thoracic trauma were reported to develop intraventricular conduction defects from 24 to 72 hours after injuries were sustained. Myocardial necrosis was demonstrated in a small number of affected cats.[40]

REFERENCES

1. Harpster NK. Feline arrhythmias: Diagnosis and management. *In* Kirk RW, Bonagura JD (eds). Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 732
2. Fox PR, Kaplan P. Feline arrhythmias. Contemporary Issues in Small Animal Practice. Vol 7 (Cardiology). New York, Churchill Livingstone, 1987, p 251
3. Fox PR, Tilley LP, Liu S-K. The cardiovascular system. *In* Pratt PW (ed). Feline Medicine. Santa Barbara, CA, American Veterinary Publications, 1983, p 249
4. Fox PR. Feline myocardial diseases. 18th Annual Waltham/OSU Symposium. Vernon, CA, Waltham USA, Inc, 1994, p 119
5. Harpster NK. The cardiovascular system. *In* Holzworth J (ed). Diseases of the Cat. Vol 1. Philadelphia, WB Saunders, 1987, p 909
6. Peterson ME, Kintzer PP, Cavanagh PG, et al. Feline hyperthyroidism. Pretreatment clinical and laboratory evaluation of 131 cases. J Am Vet Med Assoc 183:103, 1983
7. Broussard JD, Peterson ME, Fox PR. Changes in the clinical and laboratory findings in hyperthyroid cats from 1982–1992. J Am Vet Med Assoc 206:302, 1995
8. Fox PR, Peterson ME, Broussard JD. Electrocardiographic and radiographic changes in cats with hyperthyroidism: Comparison of populations evaluated during 1979–1982 vs. 1992–1993. J Am Anim Hosp Assoc (in press)
9. Fox PR, Nichols CER. Cardiovascular involvement in systemic disease. *In* Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 565
10. Fox PR. Feline myocardial disease. *In* Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 467
11. Tilley LP. Essentials of Canine and Feline Echocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992
12. Edwards NJ. Bolton's Handbook of Canine and Feline Electrocardiography. 2nd ed. Philadelphia, WB Saunders, 1987
13. Fox PR. Congenital feline heart disease. *In* Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 391
14. Hill BL, Tilley LP. Ventricular preexcitation in seven dogs and nine cats. J Am Vet Med Assoc 187:1026, 1985
15. Ogburn PN. Ventricular preexcitation (Wolff-Parkinson-White syndrome) in a cat. J Am Anim Hosp Assoc 13:171, 1977
16. Prystowsky EN, Miles WM, Heger JJ, Zipes DP. Preexcitation syndrome. Mechanism and management. Med Clin North Am 68:831, 1984
17. Sisson DD, Thomas WP. Myocardial diseases. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed, Vol 1. Philadelphia, WB Saunders, 1995, p 995

17a. Fox PR, Liu SK, Maron BJ. Echocardiographic identification of spontaneously occurring feline hypertrophic cardiomyopathy: An animal model of human disease. Circulation 92:2645, 1995

18. Liu S-K, Peterson ME, Fox PR. Hypertrophic cardiomyopathy and hyperthyroidism in the cat. J Am Vet Med Assoc 185:52, 1984
19. Jacobs G, Hutson C, Dougherty J, et al. Congestive heart failure associated with hyperthyroidism in cats. J Am Vet Med Assoc 188:52, 1986
20. Peterson ME, Keene B, Ferguson DC, Pipers FS. Electrocardiographic findings in 45 cats with hyperthyroidism. J Am Vet Med Assoc 180:934, 1982

20a. Fox PR, Moïse NS, Price RA, et al. Analysis of continuous ECG (Holter) monitoring in normal cats and cardiomyopathic cats in heart failure (Abstract). J Vet Int Med 12:199, 1998

21. Zipes DP. Specific arrhythmias: Diagnosis and treatment. *In* Braunwald E (ed). Heart Disease. A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB Saunders, 1992, p 675
22. Packer DL, Bardy GH, Worley SJ, et al. Tachycardia-induced cardiomyopathy. A reversible form of left ventricular dysfunction. Am J Cardiol 57:563, 1986
23. Sisson DD, Brown W, Riepe R. Hemodynamic effects of atrial fibrillation in dogs with experimentally induced mitral regurgitation; (Abstract). Proceedings of the 13th Annual Veterinary Medicine Forum of the American College of Veterinary Internal Medicine, 1995, p 1015
24. Mehta D, Wafa S, Ward DE, Camm AJ. Relative efficacy of various physical manoeuvres in the termination of junctional tachycardia. Lancet 1(8596):1181, 1988
25. Fisch C. Electrocardiographic manifestations of exit block. *In* Zipes DP, Jalefe J (eds). Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1990, p 628

26. Tilley LP, Liu S-K. Persistent atrial standstill in the dog and cat; (Abstract). Scientific Proceedings of the American College of Veterinary Internal Medicine, New York, 1983
27. Atkins CE, Snyder PS, Keene BW, et al. Effects of compensated heart failure on digitalis pharmacodynamics in cats. J Am Vet Med Assoc 195:945, 1989
28. Erichsen DF, Harris SG, Upson DW. Therapeutic and toxic plasma concentrations of digoxin in the cat. Am J Vet Res 41:2049, 1978
29. Wolff L, Parkinson J, White PD. Bundle branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia. Am Heart J 5:685, 1930
30. Gallagher JJ, Sealy WC, Anderson RW, et al. Cryosurgical ablation of accessory atrioventricular connections: A method for correction of the preexcitation syndrome. Circulation 55:471, 1977
31. Lown B, Ganong WF, Levine SA. The syndrome of short P-R interval, normal QRS complexes and paroxysmal rapid heart action. Circulation 5:693, 1952
32. Flecknell PA, Gruffydd-Jones ELC, Brown CM, et al. A case of suspected ventricular preexcitation in the cat. J Small Anim Pract 2:57, 1979
33. Hoffman BF, Moore EN, Stuckey JH, Cranefield PF. Functional properties of the atrioventricular conduction system. Circ Res 13:308, 1963
34. Paes de Carvalho A. Excitation of the atrioventricular node during normal rhythm. Effects of acetylcholine. *In* Dreifus L, Likoff W (eds). Mechanisms and Therapy of Cardiac Arrhythmias. New York, Grune & Stratton, 1966, p 341
35. Harpster NK. Cardiovascular diseases of the cat. Adv Vet Sci Comp Med 21:39, 1977
36. Stamoulis ME, Bond BR, Fox PR. Pacemaker therapy for symptomatic bradycardia in the cat. J Vet Emerg Crit Care 2:67, 1992
37. Fox PR, Moise NS, Woodfield J, Darke PGG. Techniques and complications of pacemaker implantation in four cats. J Am Vet Med Assoc 199:1742, 1991
38. Darke PGG, McAreavey D, Beem M. Transvenous cardiac pacing in 19 dogs and 1 cat. J Small Anim Pract 30:491, 1989
39. Colcolough HL. A comparative study of acute myocardial infarction in the rabbit, cat and man. Comp Biochem Physiol 49A:121, 1974
40. Schmökel HG, Krinke M, Meier D, et al. Intraventrikuläre Erregungsleitungsstörungen nach einem Thoraxtrauma bei der Katze. Kleintierpraxis 40:733, 1995

20

Pacemaker Therapy

N. SYDNEY MOÏSE

INDICATIONS FOR PACING

BRADYARRHYTHMIAS

Symptomatic bradycardia is the primary indication for pacemaker therapy in dogs and cats.[1–9] Although veterinary guidelines have not been established for animal pacemaker implantation, the indications are similar to those described in humans.[10] The two most common bradyarrhythmias in dogs that require pacemaker therapy are third-degree (3°) (complete) atrioventricular (AV) block and sick sinus syndrome (SSS) associated with bradycardia alone, or with the bradycardia-tachycardia syndrome (chapter 18). Less common bradyarrhythmia indications for pacing are persistent atrial standstill and high-grade second-degree (2°) atrioventricular block. High-grade block indicates that many P waves are not conducted to the ventricles (chapter 6).

Development of clinical signs depends upon many factors, including whether the bradyarrhythmia is constant or intermittent, the slowness of the associated ventricular heart rate, the overall health of the pet, and severity of underlying cardiac disease, if present. Clinical signs may include lethargy, exercise intolerance, and syncope. In some animals, congestive heart failure (CHF) can develop, causing dyspnea, tachypnea, coughing, ascites, and progressive weakness. Experimental effects of 3° AV block in dogs provide important clinical insights and implications for therapy. Ventricular dilation occurs acutely, followed by eccentric hypertrophy in chronic stages. Congestive heart failure develops after 4 months of 3° AV block. Some animals develop syncope because of poor cerebral circulation when bradycardia is intermittent and profound.

Some animals with bradyarrhythmias do not exhibit overt clinical signs at the time of physical examination. Consequently, the decision to recommend pacemaker implantation cannot be made solely on their presence or absence. One must also take into account the severity of the rhythm disorder, its likelihood to degenerate, and the potential consequences of the related worst case scenario. Frequently, owners remark that their pets display renewed energy and heightened levels of activity after successful pacemaker therapy.

WHAT DEGREE OF BRADYCARDIA REQUIRES PACING. The degree of bradycardia at which pacemaker therapy is required varies between dogs and cats, and even among canine breeds (Fig. 20–1). Cats with 3° AV block frequently have junctional and ventricular escape rhythm rates of at least 100 beats/min and sometimes exceeding 110 beats/min (Fig. 20–2). When these rates are sustained, many affected cats do not become symptomatic and may not require a pacemaker. However, cats with sustained heart rates of less than 90 beats/min are usually lethargic or may develop CHF.[11] In contrast, dogs with 3° AV block generally have ventricular escape rhythms of between 30 and 60 beats/min, and these rates may decrease over time. This same observation has been made in humans.[12] Dogs usually exhibit lethargy,

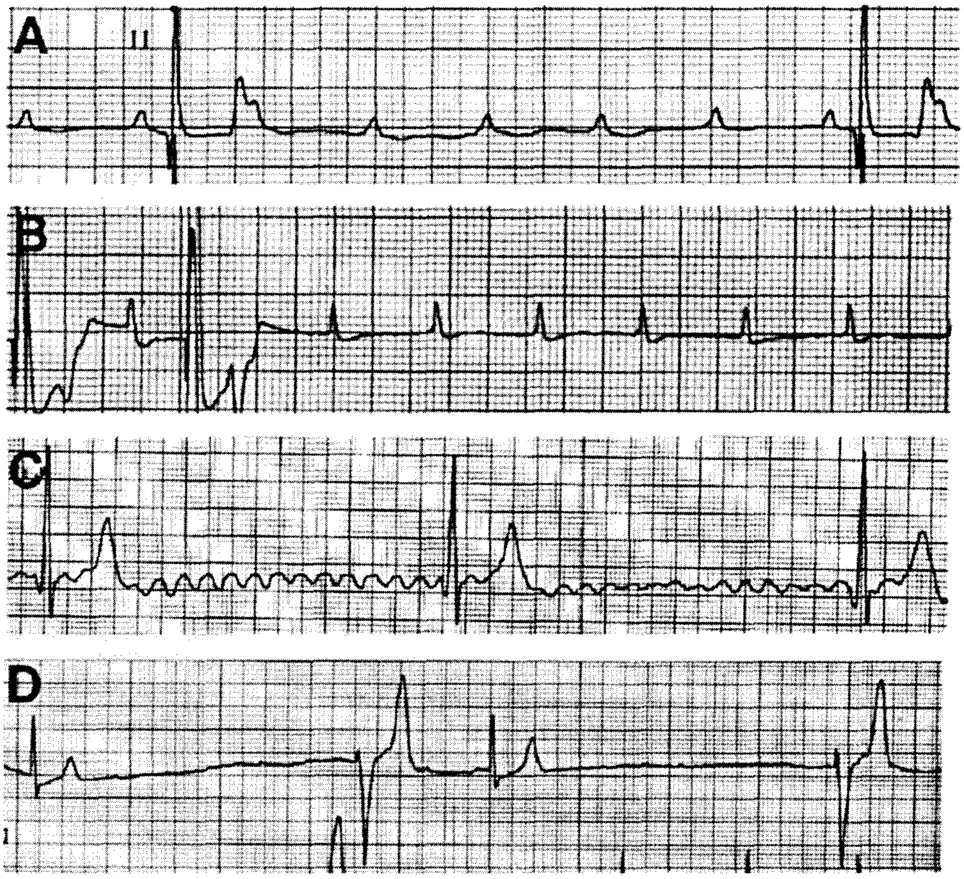


FIGURE 20–1

Electrocardiograms recorded from dogs with symptomatic bradyarrhythmias. Paper speed, 50 mm/sec. 1 mV = 1 cm. (A) High-grade second-degree (2°) AV block. The second P wave from the left conducts through the AV node, resulting in a QRS-T complex. Then, five successive P waves are blocked (nonconducted); the next (sixth) P wave again conducts and a QRS-T complex is recorded. (B) Third-degree (3°) [complete] AV block. Most dogs with 3° AV block have a stable escape rhythm greater than 30 beats/minute, although some have long periods of ventricular asystole as illustrated here. This dog experienced bouts of ventricular asystole for as long as 20 seconds, requiring emergency pacing. (C) Atrial flutter/fibrillation in this dog was associated with very slow conduction through the AV node, resulting in bradycardia and weakness. (D) Sick sinus syndrome was characterized by long sinus pauses. Ventricular escape beats rescue the heart from ventricular asystole.

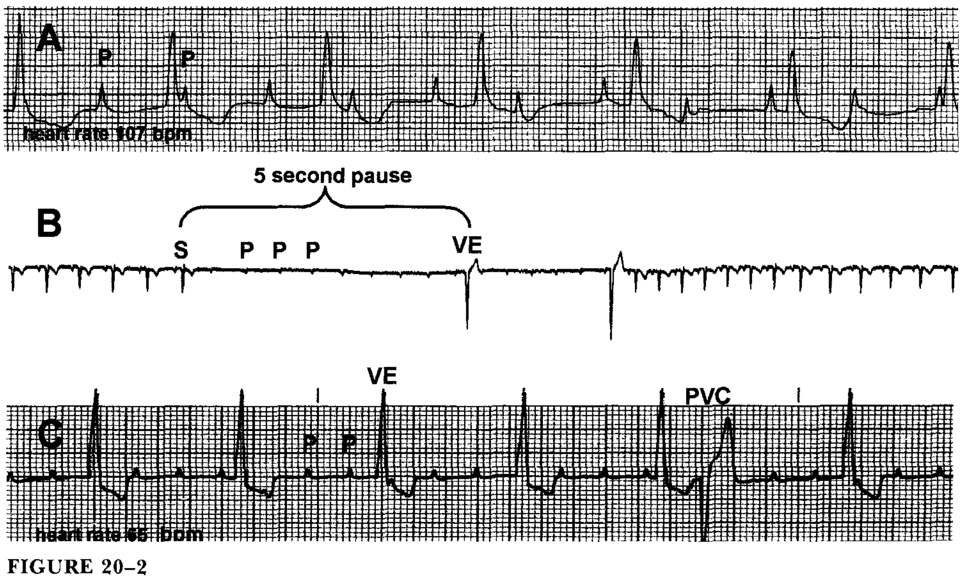


FIGURE 20–2

Electrocardiograms recorded from cats with bradyarrhythmias. (A) 3° AV block in an asymptomatic cat with a stable and consistent escape rhythm (107 beats/min). This cat did not clinically require pacing. Paper speed, 50 mm/sec. 1 mV = 1 cm. *P*, P wave. (B) Holter (24-hour ambulatory ECG) recording from a cat with frequent syncope and high-grade 2° AV block. Notice the intermittent periods without AV nodal conduction. P waves *(P)* without associated QRS complexes are seen after the sinus rhythm *(S)*. Ventricular escape complexes *(VE)* rescue the heart from a longer period of ventricular asystole. Notice the faster sinus rate that follows the prolonged ventricular pause. This occurred in response to the drop in arterial blood pressure owing to loss of cardiac output during the AV block. (C) 3° AV block in a cat with a slow ventricular escape *(VE)* rhythm and occasional premature ventricular complexes *(PVC)*. Syncope occurred every 10 minutes. The cat had underlying hypertrophic cardiomyopathy but survived without clinical signs for 10 months after pacemaker implantation. Paper speed, 25 mm/sec. 1 mV = 1 cm.

syncope, or CHF when ventricular rates are below 40 beats/min. When ventricular escape rates fall below 25 beats/min, clinical signs of low-output failure are usually severe, and these cases become emergencies requiring immediate pacemaker implantation or emergency pacing.

Often, a ventricular escape heart rate will decline over time, especially if it is low in the first place (e.g., <40 beats/min in dogs, <100 beats/min in cats). Therefore, it is the rate of the escape rhythm from subsidiary pacemakers that in part determines the critical need for pacing. Escape rhythm rates vary depending on whether they originate from junctional tissue or from more distal ventricular (Purkinje) sites. The latter has the slower rate of diastolic depolarization and therefore produces a slower heart rate.

SINUS PAUSES. The clinical significance of sinus pauses is determined by the breed of dog and the circumstances during which sinus pauses occur (see Fig. 20–1). For example, large-breed dogs during sleep normally can have sinus rates as low as 30 beats/min and sinus pauses lasting 5 seconds with only occasional ventricular escape complexes. However, such slow rates during normal activity are unacceptable. Breeds with high vagal tone (e.g., bulldog, boxer) frequently have pronounced sinus arrhythmias, with sinus pauses lasting 1 to 3 seconds at rest. Such a finding in these dogs is usually normal. In humans and cats, when an R-R interval exceeds twice the previous R-R interval, the term "sinus arrest" may apply. In dogs, even profound sinus arrhythmia may be "normal." Therefore, one should probably avoid this term in canines as it implies a pathologic rhythm. Conversely, a sinus pause longer than 2 seconds in an awake, middle-aged, female miniature Schnauzer may indicate SSS. Some dogs with SSS may go years without developing clinical signs, whereas others may have intermittent syncope associated with pauses lasting more than 8 seconds.

EVALUATION OF THE CANDIDATE FOR A PACEMAKER

DATA BASE

A complete data base should be evaluated when considering pacemaker therapy. This includes a thorough physical examination, complete blood count (CBC) and biochemical profile, electrocardiogram (ECG), thoracic radiographs, and echocardiogram, and for cats, feline leukemia virus, feline immunodeficiency virus, and serum T_4 (>6 years of age) determinations. The clinical complaint of syncope (chapter 22) may require a 24-hour continuous ECG recording (Holter monitoring) to discover what arrhythmia is present and determine whether the arrhythmia is compatible with and temporally associated with clinical signs.

SPECIFIC CANINE BRADYARRHYTHMIAS AND CONDITIONS

THIRD-DEGREE (COMPLETE) ATRIOVENTRICULAR BLOCK

The ideal candidate for pacemaker therapy is the animal whose arrhythmia is clearly associated with clinical signs and without underlying myocardial or valvular disease, such as in dogs with congenital 3° AV block. However, most animals that require pacemaker therapy are mature animals with acquired 3° AV block and possibly underlying cardiac disease. These adult animals may have other systemic, metabolic, or respiratory conditions that increase their anesthetic risk. A large LV stroke volume results from prolonged diastolic filling time combined with increased myocyte stretch. Consequently, the femoral artery pulses are exceedingly strong. The jugular veins may be distended due to right-sided heart failure, and jugular pulses may be seen when atria and ventricles contract asynchronously (atrioventricular dissociation is present with 3° AV block). Low-grade systolic murmurs may be auscultated over the mitral and tricuspid valve areas. Prerenal azotemia is often present. Radiographic evidence of variable, generalized cardiomegaly is present, depending on the duration and severity of bradycardia. Distended cranial and caudal vena cavae, hepatomegaly, or ascites may indicate right-sided or biventricular CHF. Occasionally, pulmonary edema may occur, especially if chronic, severe mitral regurgitation has been present.

Echocardiography assesses myocardial contractility and assesses valvular integrity. Cardiac chamber enlargement, higher than normal fractional shortening, effusions (pericardial, pleural, abdominal), and distended hepatic veins are common findings. Doppler echo examination may reveal right and left AV valve regurgitation. In the absence of chronic, acquired valvular disease (endocardiosis), this results from stretching the valve annulus. Diastolic mitral regurgitation is usually present with advanced AV block. The valvular regurgitation, cardiac enlargement, CHF, and prerenal azotemia usually resolve within 1 to 2 weeks after pacemaker implantation.

SICK SINUS SYNDROME

Sick sinus syndrome occurs most commonly in middle-aged to older female miniature Schnauzers. Older dachshunds and West Highland white terriers are also overrepresented. Chronic acquired valvular disease

(endocardiosis, chapter 25) is often present since affected dogs tend to be in associated age categories. Dogs with bradycardia-tachycardia syndrome, a form of SSS, may have periods of very rapid supraventricular tachycardia followed by a prolonged pause owing to overdrive suppression (see Fig. 20–1*D*) (see also chapters 6 and 18). After the pause, the femoral pulse will be of greater intensity when the escape beat breaks the protracted period of asystole. The presence or absence of valvular disease will determine radiographic and echocardiographic findings. Despite the presence of chronic acquired valve disease in many affected dogs, most respond favorably to pacemaker implantation, even if additional drug therapies are required.

PERSISTENT ATRIAL STANDSTILL

The English springer spaniel is the most common breed reported with this arrhythmia. Most affected dogs have underlying myocardial disease that affects the atria most severely. In addition, some dogs may have temporal muscle wasting. Radiographs and echocardiogram reveal biatrial enlargement. Prognosis depends to a large part on the severity of underlying myocardial disease and is often not as favorable as in other conditions requiring pacemaker therapy.

SPECIFIC FELINE BRADYARRHYTHMIAS AND CONDITIONS

Cats with primary cardiomyopathy can have high-grade 2° AV block and 3° AV block and may require pacemaker implantation.[8, 12] A number of nonreversible lesions have been described in atrioventricular conduction systems of cats with cardiomyopathies, including fibrosis, chondroid metaplasia, fatty degeneration, and osseous metaplasia.[13] In some cases the clinical need for pacemaker implantation may be overshadowed by more dominant clinical consequences of the cardiomyopathic condition, such as CHF. In other situations, cats may not exhibit clinical signs if an adequate escape rhythm is present and stable (Fig. 20–2*A*). It is important to note that high-grade 2° AV block usually progresses to 3° (complete) AV block. Thus, while the cat may be asymptomatic in the face of 2° AV block, the condition may change acutely.[8, 8a] Because these cats usually have underlying cardiac disease, anesthetic risks should be thoroughly assessed by a complete data base and echocardiographic examination. Despite this admonition, there are cats treated with pacemaker implantation that have lived for years.[8] Conduction disturbances, including advanced AV block, may be recorded in states of severe hyperthyroidism. These are commonly reversible when the euthyroid state is re-established and maintained.

ELECTROPHYSIOLOGIC FUNDAMENTALS OF CARDIAC PACING: CLINICAL APPLICATIONS

The evolution of pacing systems has been rapid. Most animals respond satisfactorily to pulse generator implantation utilizing ventricular pacing alone (i.e., VVI, see later and Fig. 20–5). However, as newer generation pacing technology becomes available to veterinarians, the use of rate-responsive pacing, synchronized atrioventricular pacing, and antitachycardia pacing will be possible. Thus, an understanding of the basic concepts for artificially pacing the heart is important in pacemaker selection, in programming, and for trouble-shooting complications. Although many animals do well after pacemaker implantation without detailed pulse generator reprogramming as described later, some will require pulse generator readjustment for optimal efficacy. This is often facilitated through technical service representatives from the pacemaker manufacturer whose devices are being implanted.

THE ENERGY FOR STIMULATION

The clinical "life" of the pacemaker pulse generator depends upon several factors involving the pulse generator and lead system. These include (1) the output voltage, (2) lead resistance, (3) pulse duration, (4) pacing rate, (5) percent pacing time, and (6) battery capacity. To induce a propagating wave of depolarization across myocytes, a certain magnitude of voltage must be applied to the heart muscle. The ability to stimulate the heart electrically is related by *Ohm's law*.

$$\mathbf{V = IR},$$

where **V** is the stimulus voltage, **I** is the current, and **R** is the total resistance to current flow. The minimum energy required to activate the heart electrically outside its refractory period is the *stimulation threshold*.[14–17] The energy of a pacing stimulus is determined by the duration of the voltage and current delivered. If excessive energy is used in stimulating the heart, the life of the pulse generator will be shortened. Therefore, optimizing for an adequate amount of energy to stimulate the heart, without wasting energy, is desirable. The *stimulus energy* **(E)** used is related to the amount of voltage **(V)**, the time **(t)** the voltage is applied, and the resistance **(R)**.[16]

$$\mathbf{E} = \frac{\mathbf{V^2 t}}{\mathbf{R}}$$

These relationships have important clinical implications in selecting the appropriate stimulus of a pace-

maker, and they can be evaluated by examination of the strength duration curve.

STRENGTH DURATION CURVE

In order for a stimulus to depolarize the heart, a certain amount of voltage must be applied for a unit of time (Fig. 20–3). The analogy of speed *(voltage)* and time *(pulse duration)* can be used to understand this relationship. For example, if an object is to reach the finish line (i.e., activate the heart), a greater speed will require less time, while a lesser speed will require more time. Therefore, to stimulate the heart to depolarize, the voltage may be set high with a shorter pulse width (duration), or low with a longer pulse width.

A *programmer* is an instrument used to change the pulse duration and the voltage to evaluate and achieve the optimal settings.[18] The relationship between the voltage and the pulse duration is exponential and is represented by the *strength duration curve* (Fig. 20–3). The curve is steep, rapidly rising with pulse duration less than 0.25 msec; in contrast, the curve is flat with pulse duration greater than 1.0 sec. The shape of this curve determines the choice of the voltage amplitude and duration of the pacing pulse. When a pacemaker is programmed, if the pulse duration is too short there is very little room for error should the *threshold for capture* increase. Thresholds for pacing can change after implantation, and such a situation may result in a loss of capture. Conversely, if the pulse width is set too long on the flat portion of the curve, the increase in the time that the stimulus is delivered has no effect

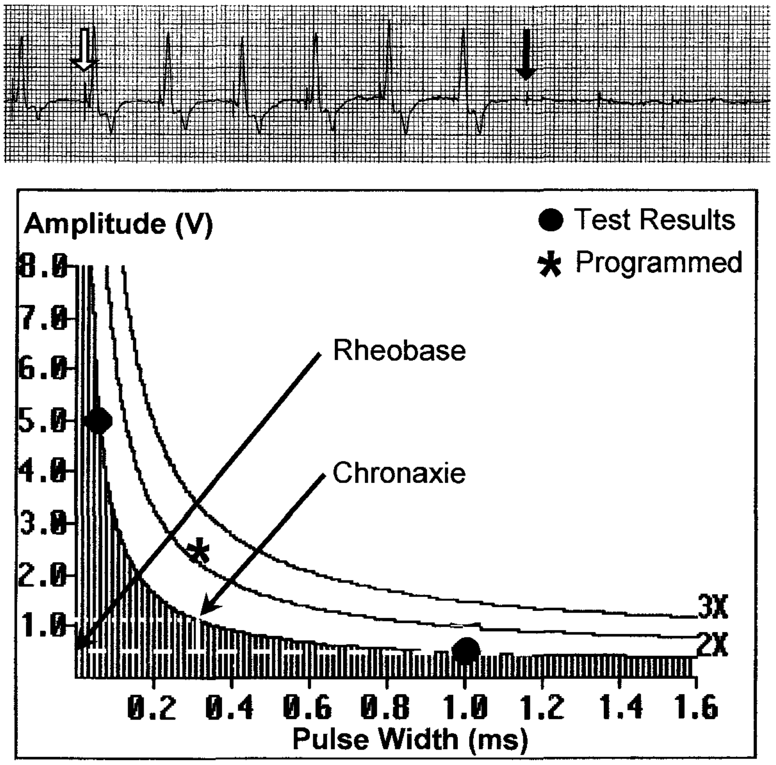


FIGURE 20–3

Top panel: ECG from an 8-year-old Saluki while permanent pacemaker pacing thresholds were being tested and the strength-duration curve was being computed. The amplitude was automatically decreased until capture was lost. Pacing spikes *(open arrow)* generated from this bipolar system gradually decreased in size. Although they are still present during ventricular asystole, they are of inadequate amplitude to stimulate the heart *(black arrow)*. Paper speed, 25 mm/sec. *Lower panel*: This was printed from the programmer following the strength-duration curve computation. The dog was paced with a Medtronic Thera DR 7940 pulse generator that was programmed in the bipolar mode. The curve formed by the edge of the shaded area is the computed curve threshold for this dog based on two measured threshold values *(black circles)*. Capture will occur with any combination of amplitude and pulse width values that are above this curve. Values below the curve will not result in capture (i.e., pacing). The two curved lines above the shaded region indicate the combination amplitude and pulse width values that will provide a safety margin of two or three times the amplitude threshold. The *chronaxie* (pulse width that corresponds to twice the rheobase) and *rheobase* (lowest voltage that results in capture at an infinitely long duration) for this dog are indicated. Pulse widths on the steep portion of the curve (less than 0.2 msec) are not recommended, because the voltage must be set so high that excessive battery drain occurs. Good settings (*) to program the pacemaker for this dog are 2.5 V at a pulse width of 0.3 ms. (Courtesy of Dr. Anna R. M. Gelzer, Cornell University.)

on capturing the heart. Instead, the excessively wide pulse duration drains the battery, and pulse generator life is shortened.

RHEOBASE AND CHRONAXIE

Two important points exist about the strength duration curve to assist in identifying optimal pacemaker programming (Fig. 20–3).[15, 19] The *rheobase* is the lowest voltage that results in capture at an infinitely long pulse duration. In modern pacemakers, this point is usually less than 1.5 msec. The *chronaxie* is the pulse width required to stimulate the heart at twice the rheobase voltage and closely approximates the point of minimum threshold stimulation energy. Although the minimum threshold is determined, a safety margin must be considered. Therefore the voltage is usually set at twice the threshold value at the chronaxie pulse width. Alternatively, the pulse width is set at three times the chronaxie pulse width provided the pulse width threshold is less than 0.2 msec. If it is greater than 0.2 msec, then the lead should be repositioned or voltage increased. Also, if high voltages are required (e.g., > 5 V), repositioning of the lead is advised. Manufacturers usually recommend that chronic leads should not have stimulation thresholds greater than 2.5 V pulse amplitude at a pulse width of 0.5 ms. Such high voltages greatly reduce the longevity of the pulse generator. Ultimately, some adjustment in both the voltage and the pulse width is usually performed to optimize safety while preserving battery longevity.[19]

The strength duration curve is generated initially after pacemaker implantation and on recheck examination.[19–22] The standard method is to have the heart pacing, to decrease the voltage at a given pulse width until capture is lost, and then to decrease the pulse width at constant voltage. The procedure is repeated until enough points are generated to create the curve (Fig. 20–3). Depending on the pacemaker and the programmer, this can be done manually or automatically. Capture *hysteresis* (Wedensky's effect) usually exists such that the testing is done from capture to the loss of capture, and not from lack of capture to capture.[23] Greater energy is required to gain capture, and thus the curves generated would be different.

The threshold for consistent pacing can change over time and is dependent on the type of lead used (e.g., passive, active, porous, steroid-eluting).[16] With nonsteroid-eluting leads, thresholds rise during the first week, compared with implantation values, and then stabilize 6 weeks after implantation. The lead elicits a foreign body response, with cellular infiltrate, edema, and finally a collagenous capsule. Beyond the capsule, myofibril disarray develops. The precise response depends again on the type of lead tip. If a lead is unstable, more inflammation and fibrous tissue can develop. This can result in deterioration of stimulation thresholds. Studies in dogs with nonsteroidal-eluting corkscrews have shown that thresholds are similar regardless of the location of the electrode tip.[16]

PACING THRESHOLDS

To determine whether the position of the pacing electrode is adequate, *pacing thresholds* ideally are determined at the time of implantation.[19, 22] However, until recently such determinations have not been routinely performed in animals. An external testing device is used, known as a *pacing system analyzer*, or PSA. The threshold is determined in volts at a pulse width of 0.5 msec. The PSA is set at 5 V. The pacing rate is increased until the heart is consistently captured. Then the voltage is gradually decreased until a loss of capture occurs (usually less than 1 V at 0.5 msec for the ventricle at the time of implantation). If high voltage is needed to capture the heart, a different lead position in the right ventricle is sought.

THE IMPORTANCE OF IMPEDANCE

Impedance is the total resistance to current flow.[15, 24–26] Ideal impedance will allow for proper current flow for myocardial stimulation yet be high enough to deter unnecessary current drain on the pulse generator. Total pacing impedance is determined by (1) resistance of the conducting lead (conductor resistance), (2) resistance between the electrode and tissue (electrode resistance), and (3) resistance caused by the accumulation of charge at the electrode tip interface (polarization resistance).[15, 26] Excessive resistance in the lead generates heat and is inefficient at generating current for pacing. A small electrode tip offers higher resistance but concentrates the current at the point of implant for more efficient use of energy. Polarization can be minimized by not using excessively long pulse widths and electrodes with small tips. Impedance can be measured, and it changes after implantation (in nonsteroidal-eluding leads). Initially, impedance falls during the inflammatory phase but then rises to a stable level. Bipolar leads tend to have higher conductor impedance than unipolar leads because two conducting wires are required. Also, unipolar pacing has lower total impedance because of the large surface area of the anode (pulse generator).[26]

The lead impedance is normally between 250 and 1000 ohms. Most lie between 500 and 700 ohms at the nominal pacemaker setting of 5 V.[26] At the time of implantation and during follow-up examination, the lead impedance ideally should be determined. Moreover, complications of lead fracture, insulation breakage, or lead dislodgment can be evaluated by determining the lead impedance. Lead impedance should remain constant over time or decrease minimally. Elevations in the lead impedance (> 1200

ohms) with elevations in the voltage threshold are compatible with lead fracture. Conversely, insulation breakage is associated with low or normal voltage thresholds and low impedance (< 250 ohms). A lead dislodgment or exit block is associated with high voltage threshold and normal lead impedance.

SENSING

Although constant pacing is usually required for animals with 3° AV block, the ability to sense inherent rhythms in animals with high-grade 2° AV block and SSS is important for safety. Avoidance of pacing during the vulnerable period in the T wave is essential in the prevention of ventricular fibrillation. Also, improved hemodynamics and preservation of battery life occur when an inherent sinus rhythm is allowed to dominate. The ability to sense an inherent rhythm is dependent upon several factors. These include (1) the type of lead (unipolar versus bipolar), (2) electrode size, (3) lead contact to the myocardium, (4) tissue reaction around the electrode, (5) position of the electrode, (6) physiologic factors (respiration, exercise, catecholamines, body position), and (7) drugs.[16, 20, 21]

Certain determinants of sensing are programmable. These include (1) amplitude, (2) filtering, and (3) slew rate of the intracardiac electrogram recorded under the tip of the implanted lead. When the sensitivity is increased, the numerical value (mV) or amplitude of the electrogram that is able to be sensed is reduced—that is, the pacemaker is more sensitive and detects smaller (lower-amplitude) ECG signals (complexes). When the sensitivity is decreased, the numerical value or amplitude of the electrogram that is able to be sensed is increased. That is, the pacemaker is less sensitive and detects only larger (high-amplitude) ECG signals (complexes). This prevents the oversensing of waveforms such as the T wave or myopotentials. Ideally, the sensitivity of the pacemaker should be programmed to twice as sensitive as the value of the sensing threshold (the numerical number to program will be half the threshold number).[19] Because determining the sensing threshold requires that the animal have an adequate escape rhythm, determination of sensing threshold may not be possible.

Filtering of the intracardiac signal plays a critical role in the sensing of the electrogram.[15, 21] Low-frequency signals such as the T wave or very-high-frequency signals such as myopotentials must have higher amplitudes to be sensed. The ventricular signal from the intracardiac electrogram is large at 6 to 15 mV or more and is usually not difficult for the pacemaker to sense. In contrast, sensing the atrial electrogram can be more difficult and requires greater sensitivity than ventricular sensing owing to the smaller amplitude of 1.5 to 2 mV.

Another determinant of sensing is the *slew rate*, the slope or rate of change in the voltage.[15, 21] Complexes with gradual increases in amplitude (low slew rate) are more difficult to sense, even though the sensitivity amplitude is programmed correctly. However, if the amplitude is large, slew rate is of lesser importance.[19] The amplitude and slew rate do change after implantation. Therefore, adjustments to sensing may be needed during follow-up examinations.

Although modifications are made in the amplitude and filtering for proper sensing, a certain blanking and refractory period after a sensed complex must be programmed to improve signal discrimination.[21] This is done to avoid oversensing the T wave of the paced or sensed complex. The *blanking period* lasts for 25 to 100 msec after the pacing spike, and the *refractory period* is programmed to adjust to the patient's QT interval. However, if the refractory period is too long, then the pacemaker has the potential not to sense premature complexes (Fig. 20–4). Alternatively, if the refractory period is too short, T-wave sensing is a problem. Atrial sensing requires that the refractory period be longer to avoid sensing the far-field ventricular electrogram.

PACING EQUIPMENT

PACEMAKER MODALITIES

Pacemakers are coded by a 3- to 5-lettering system (Fig. 20–5) that denotes the site and mode of pacing.[19] The first letter position denotes the *chamber paced*, and the second position denotes the *chamber sensed* (V, ventricle, A, atrium). The third position denotes whether the *mode of response* to sensing is inhibited (I, inhibited)—that is, pacemaker discharge is suppressed by a sensed signal, or triggered (T, triggered)—that is, pacemaker discharge is triggered by a sensed signal, both (D, dual or both), or none (0, none). The fourth position indicates *programmability* (0, none; P, simple programmable; M, multiprogrammable; C, communicating; R, rate modulation). A multiprogrammable pacemaker is ideal. The fifth position indicates whether *antitachyarrhythmia function* is available.

Therefore, VVI pacing indicates that the pacemaker is programmed to pace the ventricle and sense ventricular complexes; when these complexes are sensed, the pulse generator is inhibited from firing. This type of pacing is the one most commonly used in veterinary medicine. However, it may be better to dual-chamber-pace (DDD or DDI) or atrial-pace (AAI) dogs with SSS (see Complications later). The more sophisticated and complicated pacing modalities, such as (AV) sequential pacing, have until recently required two leads, which increases the possibility of lead dislodgment.

Another feature that is incorporated into some pace-

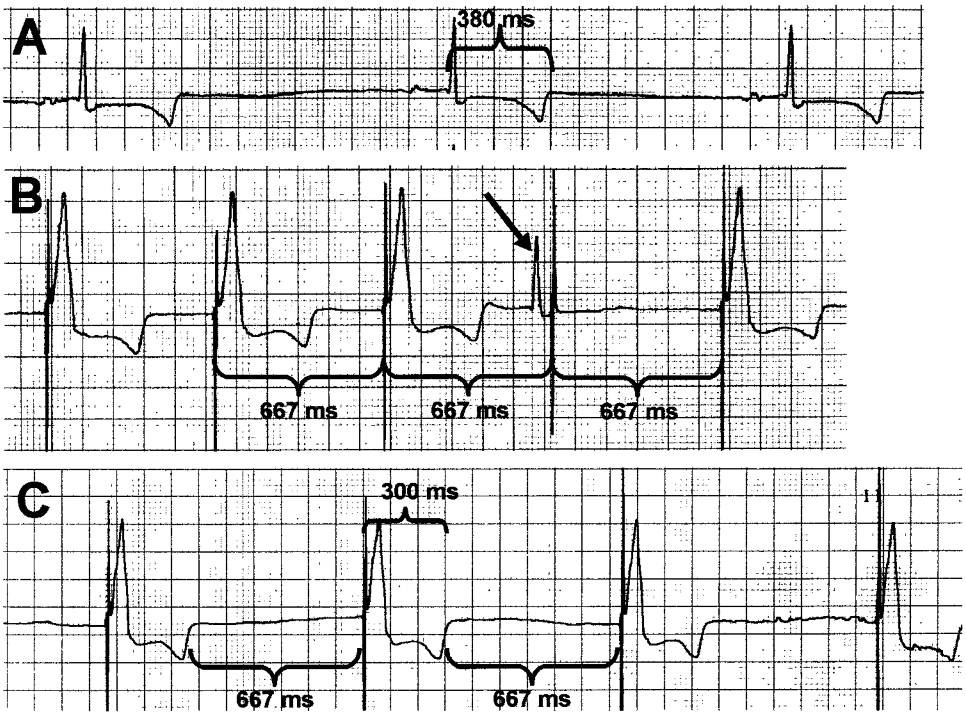
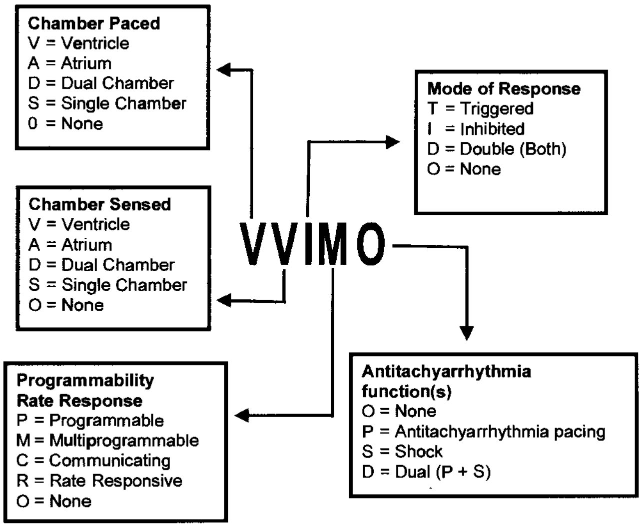


FIGURE 20–4

Electrocardiograms recorded from a West Highland white terrier with sick sinus syndrome. The dog had long periods of marked sinus bradycardia and intermittent periods of rapid supraventricular tachycardia. Paper speed, 50 mm/sec. 1 mV = 1 cm. (A) Initial ECG shows sinus bradycardia and a prolonged QT interval (380 ms) related to the slow heart rate. (B) This pacemaker, programmed for a rate of 90 beats/min (RR interval, 667 msec), failed to sense the spontaneous complex *(arrow)*, indicating an undersensing problem. (C) The refractory period (220 msec) and sensitivity (2.5 mV) were changed, but then the pacemaker oversensed the T waves. This is because the programmed refractory period was too short, allowing the T wave to be detected. Note that the interval of 667 msec *(ms)* now begins at the T wave. The refractory period was reprogrammed to 325 ms.

FIGURE 20–5

Codes used for describing the capabilities of a pulse generator. VVIMO indicates that the chamber paced is the ventricle, the chamber sensed is the ventricle, the mode of response is inhibited, the pacemaker has multiple parameters that can be programmed, and there are no antitachycardia features with this device.



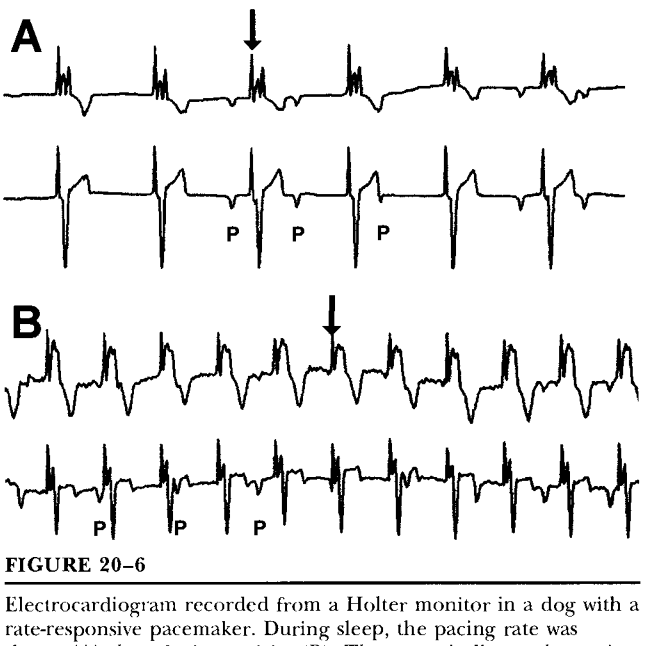


FIGURE 20–6

Electrocardiogram recorded from a Holter monitor in a dog with a rate-responsive pacemaker. During sleep, the pacing rate was slower (A) than during activity (B). The arrow indicates the pacing artifact spike. P, P waves.

makers is *rate modulation.*[27–29] Instead of the rate being fixed and the only alteration to that rate being the sensing of an inherent rhythm, the pacing rate changes with physiologic needs (Fig. 20–6). The pacing rate can be programmed for a lower and an upper limit. Rate-modulated pacemakers change the pacing rate based on right ventricular volumes or pressures, blood temperature, oxygen saturation or pH, ventilation, or numerous ways of activity sensing. Activity sensors are the most successful and have been widely tested in humans.[27]

EXTERNAL TEMPORARY PACEMAKERS

External temporary pacemakers provide endocardial pacing. They are intended for short-time use to stabilize the patient or during the anesthetic induction for permanent pacemaker implantation.[30] They also allow the rate, voltage amplitude, and sensitivity to be selected prior to permanent pacemaker implantation. Temporary pacing can be accomplished by three routes: transvenously, transcutaneously, or transesophageally. The transvenous route is used most commonly in dogs. External temporary pacemakers are bipolar, with a positive and a negative port to connect the pacing lead. Many different electrophysiologic leads can be used for temporary pacing, including quadripolar catheters (i.e., four electrodes spaced over the last couple of centimeters of the catheter). A no. 5 French pacing catheter (lead) is used most commonly with the temporary pacemaker. This size of lead is adequate to stay in contact with the endocardium, but it is not too stiff that it risks inadvertent puncturing of the right ventricular (RV) wall.

The actual necessity of temporary pacing during permanent pacemaker implantation is controversial and depends on the individual patient. Animals with slow unstable escape rhythms (< 30 beats/min in dogs, < 90 beats/min in cats) or with variable escape rhythms with long, intermittent periods of ventricular asystole may be best served with the insurance of temporary pacing. Moreover, dogs with SSS have volatile responses to anticholinergic drugs. Occasionally the heart rate speeds rapidly, only to be followed by more profound periods of asystole as the overdrive suppression has excessively repressed subsidiary pacemakers. Arguments against the use of temporary pacing include increased surgical time, necessity for heavy sedation; and lack of clear necessity for temporary pacing; and if a jugular vein is used for temporary lead placement, this vessel then becomes unavailable for permanent endocardial lead placement should a problem develop in the opposite jugular vein during permanent pacemaker implantation procedure. However, temporary pacing affords a margin of safety should problems develop, and problems may sometimes occur despite careful preparation. To avoid the use of the second jugular vein and improve venous access with the least amount of sedation, we routinely use percutaneous instrumentation with an introducer via the femoral vein (see Procedure later). Temporary pacing in cats is technically difficult, and therefore this step is frequently bypassed.

PERMANENT PACEMAKERS

The pacing *pulse generator* houses the battery (power source), lead connection, and programming electronics and is generically referred to as the "pacemaker." These devices are manufactured by a number of companies. Modern pulse generators derive energy from a lithium-iodide cell with an inherent voltage, when new, of 2.78 volts (this is not the same as output voltage amplitude).[15] A new pulse generator may have a clinical longevity of 7 to 14 years, depending on the enacted programming. Advancements in this field have continued rapidly, with modern pulse generators being quite small with multiprogrammable features.

In veterinary medicine, pacemakers are rarely purchased at their retail market value because of their high cost and the lack of third-party insurance reimbursement. Instead, most are obtained from pacemaker companies as "seconds" that have minor superficial defects, that are surplus units being replaced by newer technology, or occasionally that are explanted from humans or originate as demonstration models. The pulse generator and lead must be gas sterilized. Currently, pacemakers and leads can be purchased

through CANPACERS, which is organized through the American College of Veterinary Internal Medicine, subspecialty of Cardiology.

The battery end-of-service indication can be identified in several ways.[24] The clinical indicators of a declining pulse generator include (1) a change in the pacing rate to the predetermined fixed rate or a 10 percent drop in the programmed nonmagnet rate, (2) a drop by 20 percent of the magnet rate (see later), or (3) an increase in the pulse width. Alternatively, examination of a telemetrized pulse generator can give an indication of the voltage (end-of-service voltage is 2.6 V) or of the battery impedance (increased impedance exists at the end-of-service). Programmers will state the message of the end-of-service.

UNIPOLAR VERSUS BIPOLAR PACING

The number of *electrodes* in contact with the heart is denoted as *unipolar* (one electrode in contact with the heart) or *bipolar* (two electrodes in contact with the heart) (Fig. 20–7).[26] Pacemakers can be exclusively unipolar with a unipolar lead, be bipolar, or be programmed to either unipolar or bipolar with a lead that can function in either mode. That is, a modern bipolar pulse generator and lead frequently can be programmed to operate as a unipolar system. However, a unipolar pulse generator and lead can operate only as a unipolar system. Unipolar and bipolar pacing both require an anode (positive) and a cathode (negative) pole. The cathode in each is the tip of the lead. The anode of a unipolar system is the pulse generator case, whereas the anode in the bipolar system is located proximal to the cathode on the lead and positioned in the heart.

Unipolar pacing has a *pacing artifact* that is substantially larger than that of bipolar pacing (Fig. 20–7) and is more susceptible to oversensing and inhibition by skeletal muscle potentials. Skeletal muscle stimulation is more likely than with bipolar pacing. Because unipolar pacemakers can stimulate local skeletal muscle, placement of the pulse generator in a pocket deep to skeletal muscle can lead to "thumps" or jerking of the muscle tissue in the region of the implantation. Thumping can be notable if the voltage amplitude is programmed high. It is important to note that for a unipolar pacemaker to pace, the uninsulated side of the pulse generator must be in contact with the tissues.

Bipolar pacing has a pacing artifact that is substantially smaller than that of a unipolar pacing system and is less susceptible to oversensing and inhibition by skeletal muscle potentials. Skeletal muscle stimulation is less likely than with unipolar pacing. Newer technology has made bipolar leads more flexible, and, therefore, bipolar pacing is increasingly more common than unipolar, thus avoiding some of these problems.[26] With a bipolar system, the pulse generator does not require tissue contact for pacing.

PACEMAKER LEAD SYSTEMS

The pacing lead consists of the *conductor* (coil of wire that conducts the current from the pulse generator to the stimulating electrode), *lead insulation*, and *lead connector* (Fig. 20–7). Continuous development of leads over the past two decades has resulted in the production of many types by numerous manufacturers. The practical necessity to acquire pacing pulse generators and pacing leads at reasonable prices often results in having an inventory of assorted components that are not compatible. Some leads of older manufacture have sealing rings set at different points such that they do not allow the use of one brand of lead into another brand of pulse generator. Some incompatibility can be resolved with the use of connection adapters. Recently, standardization has been pushed in the industry for shared compatibility between brands of pulse generators and the leads.[10, 31]

Older leads have 5- to 6-mm connectors with bifurcated bipolar connections. Newer lead connectors are smaller, and bipolar connectors are now low-profile, not bifurcated, and as small as unipolar connectors.[26] The industry standard for newer leads is designated as IS-1 UNI for unipolar leads and IS-1 BI for bipolar leads. However, when confronted with leads that are not of this standard, compatibility of a given lead with a given pacemaker can be determined by (1) consulting with the customer service department of a pacemaker manufacturer, (2) looking up the pulse generator and lead in references such as the Pacemaker and Connector Encyclopedia or The Medtronic Guide to Lead Adapters and Battery Depletion Indicators, published by Medtronic in 1996. Such references are actively updated, and, it is hoped, they will soon be available on-line. The new leads can be adapted to older pulse generators with the use of an adaptive sleeve. It should be emphasized that the compatibility and polarity of the lead and pulse generator should be double-checked before surgery.

Endocardial leads may have active or passive fixation. Active fixation leads penetrate the myocardium with a screw whereas passive fixation leads entangle the trabeculae with tined tips. Both are equal in the frequency of dislodgment (Lehmkuhl L., personal communication, 1998). In human medicine, dislodgment is less than 1.5 percent for ventricular leads and less than 5 percent for atrial leads. In veterinary medicine, lead dislodgment is approximately 10 percent (Lehmkuhl L., personal communication, 1998). The high incidence in veterinary medicine may be due to the lesser experience of the operator and the

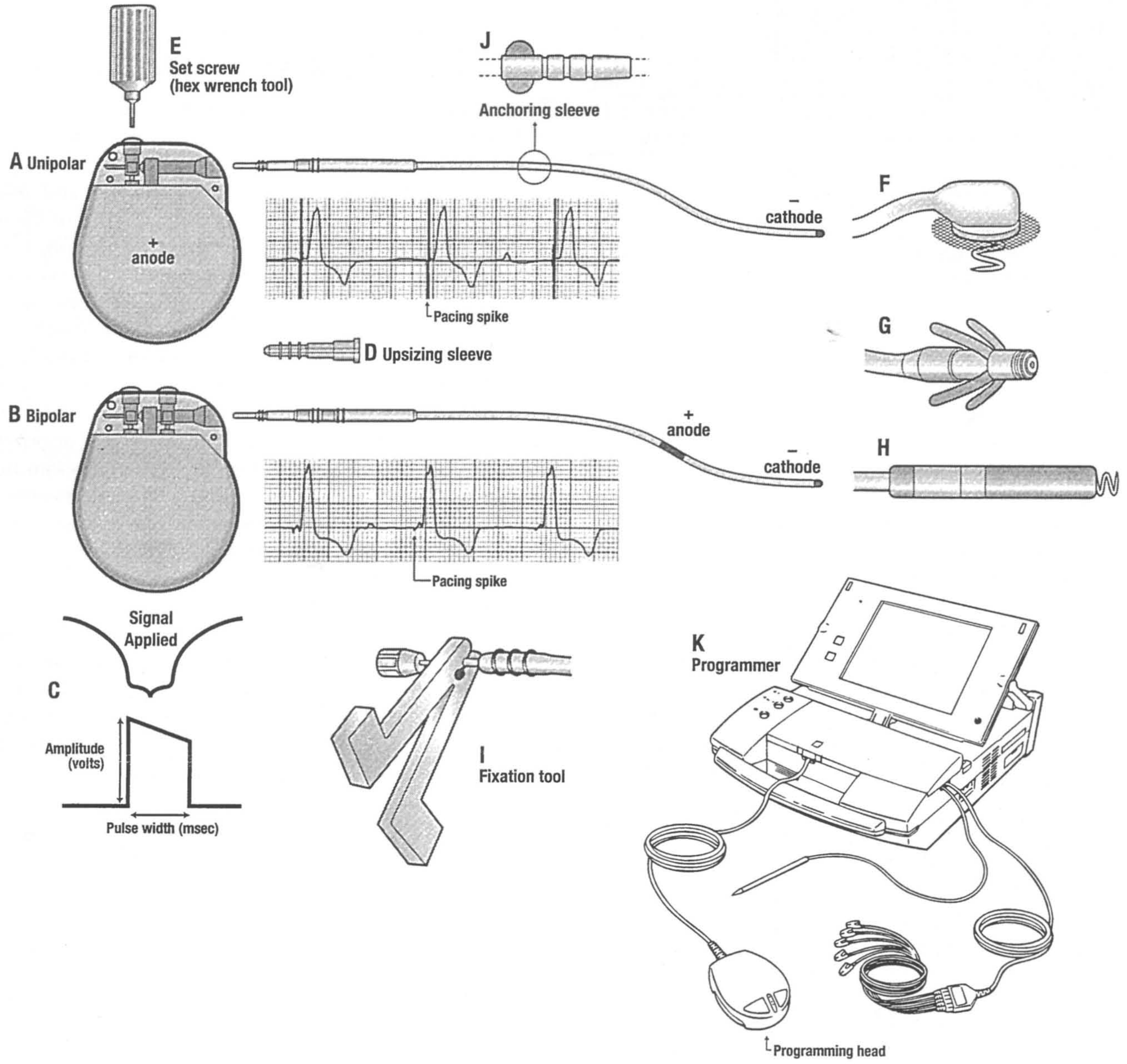


FIGURE 20–7

Some of the equipment used in the implantation of a cardiac pacemaker. (A) A unipolar pulse generator: the pulse generator case is the anode and the pacemaker lead tip is the cathode. The lead has a single connecting point to the pulse generator. The ECG from a unipolar pacemaker has a large pacing spike artifact. (B) A bipolar pulse generator: the anode and the cathode are situated distally on the pacing lead. The lead has two points connecting to the pulse generator (notice two setscrews versus one in the unipolar system). The ECG from a bipolar pacemaker has a small pacing spike artifact. (C) The pulse generator produces an electrical current of a given voltage for a given amount of time. These parameters can be programmed. Some leads and pulse generators do not match but can be adapted with either an upsizing (D) or downsizing sleeve. To connect the lead with or without the sleeve, a setscrew or hex wrench tool is used (E). The leads (most commonly) can be (F) epicardial, (G) tined endocardial, or (H) screw-in endocardial types. When the screw-in endocardial lead is secured to the endocardium, the fixation tool (I) is turned to advance the helix. Once the endocardial lead (tined or screw-in) is positioned, it is sutured to the vein with an anchoring sleeve (J). A programmer (K) can be used to adjust and test the quality of pacing. Not shown is the pacing system analyzer (PSA) or a temporary pacemaker.

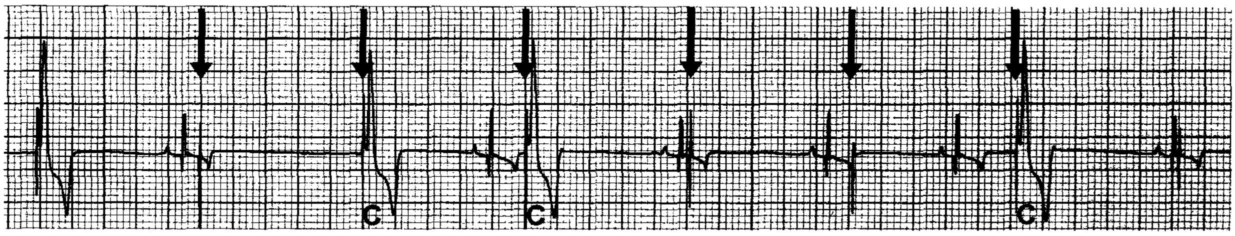


FIGURE 20–8

ECG recorded from a dog with sick sinus syndrome whose pacemaker was being interrogated. The programmer was put in "magnet mode," which caused the pulse generator to pace in the VOO mode. That is, the ventricle was paced at a fixed rate without sensing. Notice that the pacing spikes are spaced consistently and irrespective of the underlying inherent rhythm. It is important to remember to remove the magnet or turn it off when evaluating a newly programmed setting. *C*, captured beats.

movement of animals, compared with that of humans, during the initial implantation period.

PACEMAKER PROGRAMMER

Modern pacemakers allow pacing parameters to be noninvasively programmed during or after implantation by telemetry.[18] Some pacemakers have limited ability to be programmed, such that only heart rate, amplitude, and pulse width can be changed. These pacemakers will have fixed refractory periods, blanking periods, and upper limit heart rates. We have found that the ability to program the refractory period is important in dogs and cats. Newer models have greater flexibility and are multiprogrammable (e.g., refractory period, rate modulation, polarity). Furthermore, newer models allow automatic or manual testing of thresholds for stimulation and sensing (see Fig. 20–3). Each manufacturer that makes pacemakers also makes programmers. Unfortunately, these are not interchangeable among different manufacturers. The software of new programmers can be updated so that new pacemakers may be programmed. Programming devices often can be borrowed from the pacing companies or local sales representatives. Alternatively, the local sales representatives will assist in programming during implantation or during follow-up examination. The ability to program a pacemaker specifically greatly enhances its performance. In general, the instruction manuals that accompany modern programmers are complete and written to be clinically understandable.

PULSE GENERATOR INTERROGATION AND REPROGRAMMING. By placing the programming head over the implanted pulse generator, the pacemaker can be evaluated.[26] An interrogation command is triggered, and the programmer communicates with the pacemaker to identify the specific model, serial number, and programming of the pulse generator. Held over the pacemaker, an electrogram recorded from the implanted lead can be viewed on the screen of the programmer and printed. A simultaneous surface ECG also can be recorded. A keyboard or touch-screen prompts can change parameters. These instructions and the old values can be printed for verification. Also, the pacemaker is interrogated following the reprogramming to check the values.

The programming head also contains a magnet. An option exists to turn the magnet on or off. If left in the "on" position, the pacemaker will pace the heart in the VOO mode such that fixed pacing occurs without the sensing of inherent rhythms (Figs. 20–5, 20–8). To evaluate the effects of a new program setting, the wand must be removed from over the pulse generator or the magnet turned off, otherwise pacing continues in the nominal fixed VOO mode, and evaluation of new settings cannot be made.

HEMODYNAMICS OF PACING

SEQUENTIAL CONTRACTIONS OF THE ATRIA AND VENTRICLES

Single-chamber (ventricular, VVI) pacing is used almost exclusively in animals because of its simplicity and acceptable results in most cases, although AV sequential pacing is physiologically superior. Atrial contraction may contribute 15 to 25 percent to cardiac output. With VVI pacing, the loss of the normal atrial contribution to filling, followed by ventricular contraction, can reduce systemic blood pressure and cardiac output in some individuals. However, most animals do not incur a significant drop in blood pressure with ventricular pacing (Fig. 20–9), probably because of increased sympathetic activation that compensates for the divergent cardiac depolarization. A resultant increase in peripheral vascular resistance is a normal physiologic response to ventricular pacing.[32] However, a critical evaluation of dogs after pacemaker implantation has not been conducted. Furthermore, single-

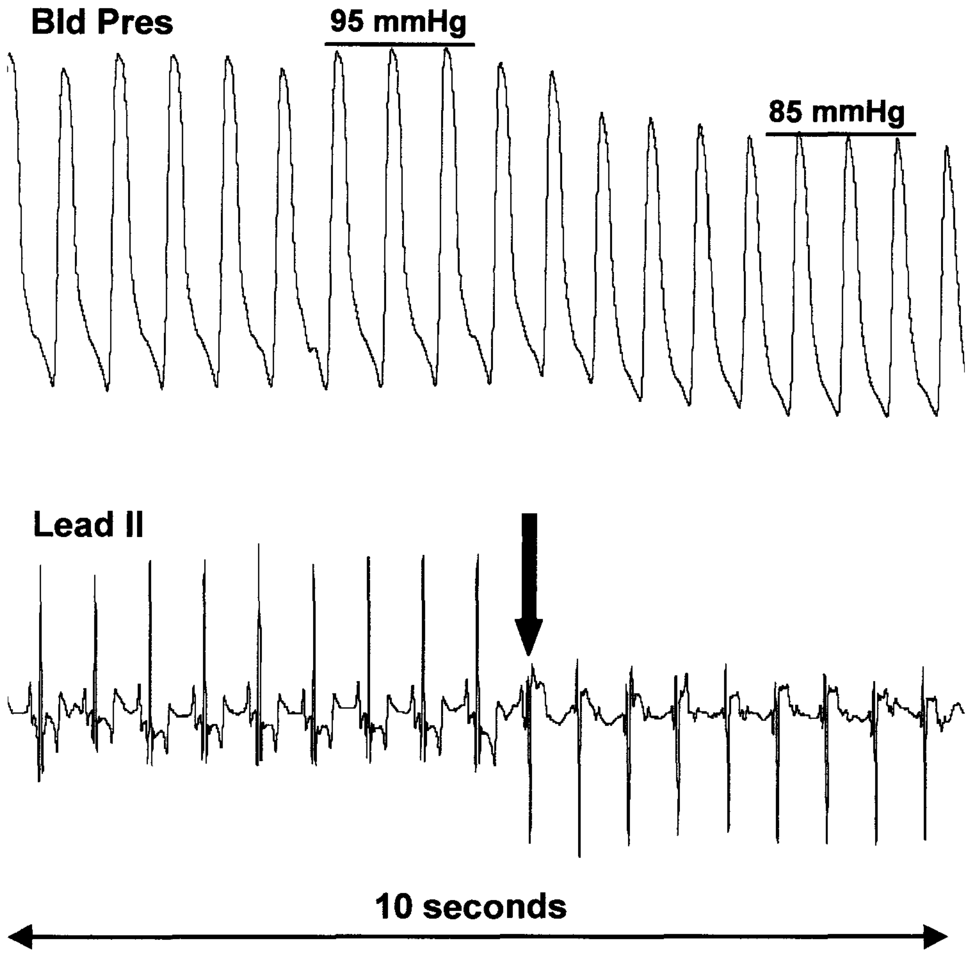


FIGURE 20–9

Arterial blood pressure *(Bld Pres)* recorded from a dog during sinus rhythm and then after ventricular pacing *(arrow)* at a similar rate. The blood pressure drops approximately 10 mmHg. In humans, a drop greater than 20 mmHg is considered a risk factor for the development of pacemaker syndrome.

chamber pacing of the atria (AAI and AAIR) in dogs with SSS and a competent AV node warrants consideration.

The superiority of AV sequential pacing to simulate the normal contribution and timing of atrial contraction has been experimentally established in the dog. The percentage augmentation by atrial systole over ventricular pacing alone increases with higher pacing rates,[33, 34] although AV synchrony is of lesser importance at high levels of exercise.[19] Elevations in atrial pressures occur with ventricular pacing alone, compared with AV sequential pacing. This is primarily caused by atrial contraction against closed AV valves. The atrial distention associated with VVI pacing stimulates the release of atrial natriuretic peptide (ANP) from the atria.[35] The ANP, which causes vasodilation and diuresis, counteracts the baroreceptor stimulation that occurs with the drop in blood pressure present with ventricular pacing. In addition, cardiac sympathetic activity, as evidenced by elevations in plasma and coronary sinus levels of norepinephrine and epinephrine, is greater with VVI pacing compared with AV sequential pacing.[36]

Further studies in dogs with experimental 3° AV block reveal that VVI pacing and atrial systole against closed AV valves causes a reversal of blood flow and pulmonary venous regurgitation.[37–39] Such changes can exacerbate or contribute to congestive heart failure. For this reason, dogs with SSS ideally should be allowed to have their inherent rhythms dominate when the rate is adequate (Fig. 20–10). Although these physiologic changes argue for the superiority of atrioventricular sequential pacing, the current technical complexities in implantation make it a more difficult procedure compared with the simpler ventricular pacing technique.

VENTRICULOATRIAL CONDUCTION

Retrograde depolarization of the atria (ventriculoatrial [VA] conduction) is a potential complication of ventricular pacing. It occurs in approximately 90 percent of humans with SSS and 30 percent with AV block.[40] Clinical impressions of dogs with SSS support a similar pattern of VA conduction and may result in antegrade reactivation of the ventricle (Fig. 20–11). The long-term effects of VA conduction in dogs have not been established, but humans with consistent VA conduction have the highest susceptibility to adverse

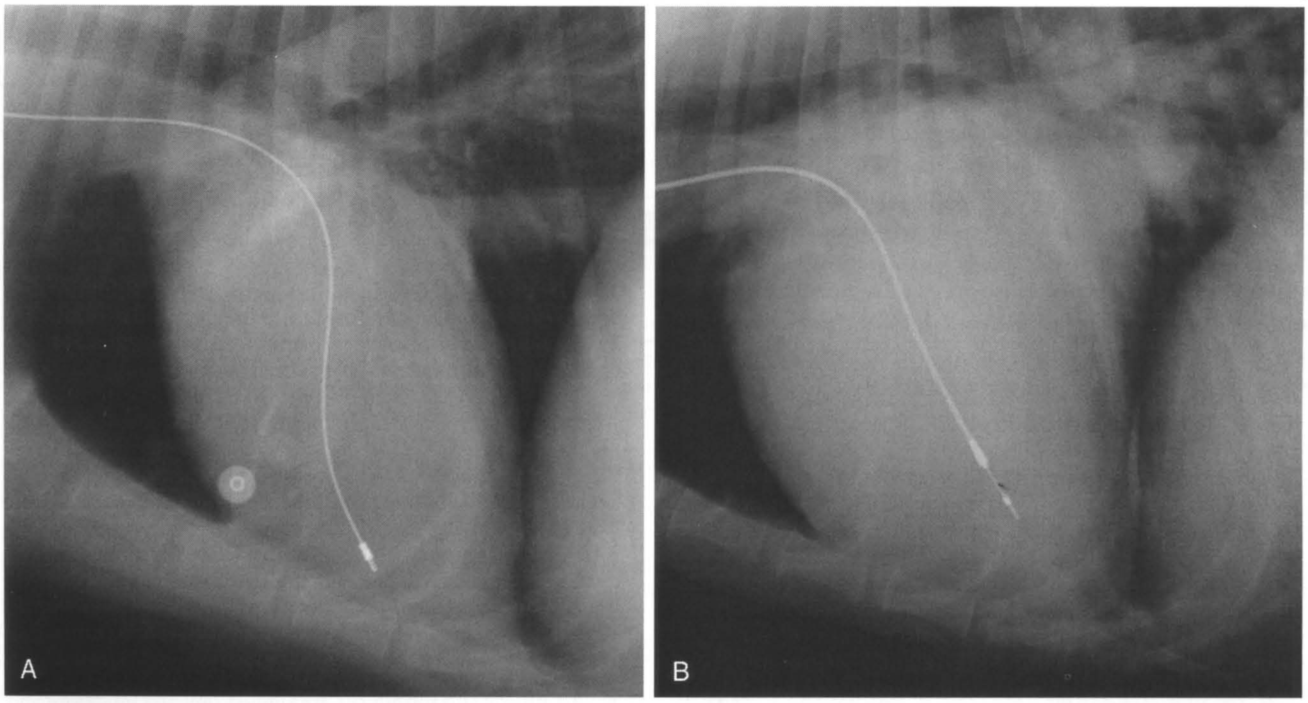


FIGURE 20–10

Right lateral radiographs of a dog in 3° AV block. (A) The cardiac silhouette is normal in size and shape. A permanent pacemaker and endocardial pacing lead have just been implanted. The circular opacity at the cranial sternal border is an ECG electrode affixed on the skin. (B) Over the next 9 months, the dog developed cardiomegaly, myocardial failure, and, ultimately, congestive heart failure. The pacemaker malfunctioned, with late-onset intermittent loss of capture, which became progressively worse. Notice that the endocardial lead appears to have become displaced away from the apex when compared with (A); however, fluoroscopy and impedance evaluations confirmed that the lead was securely attached. A diagnosis of loss of capture—due either to exit block or progressive myocardial disease—was made.

FIGURE 20–11

Electrocardiograms recorded from two miniature Schnauzers with sick sinus syndrome. (A) Retrograde, nonconducted P waves *(rP)* are seen. This indicates ventriculoatrial (VA) conduction. The arrow indicates the pacing artifact from the pulse generator programmed in the bipolar mode. (B) The VA conduction in this dog results in a retrograde P wave *(rP)* that subsequently reactivates the ventricle (notice the QRS-T complexes that follow each rP). The arrow indicates the pacing artifact from the pulse generator programmed in the unipolar mode. Paper speed, 50 mm/sec. 1 mV = 1 cm.

circulatory reflexes, which are initiated by atrial receptors.[34, 41, 42] Distention of the atria, pulmonary veins, and venoatrial junctions stimulates vagal afferents, which causes a vasodepressor response with a decrease in mean arterial blood pressure and heart rate, as well as withdrawal of sympathetic vasoconstriction.[34, 42] The presence of VA conduction is associated with greater elevation of right-sided heart and pulmonary filling pressures. Additionally, cannon A waves and atrial distention are greater than without VA conduction.[37] During periods of increased sympathetic tone, such as exercise or stress, VA conduction is more likely.

PACEMAKER IMPLANTATION

ANESTHESIA

There is no consensus regarding an optimal anesthetic protocol. Modern balanced anesthesia techniques provide safe, yet varied, methods (chapter 38). Three commonly used protocols include (1) premedication with morphine and glycopyrrolate, induction with ketamine and diazepam, and maintenance with isoflurane; (2) premedication with morphine and acepromazine, induction with etomidate, and maintenance with isoflurane; or (3) premedication with morphine, glycopyrrolate, and oxymorphone, induction with ketamine and diazepam, and maintenance with isoflurane. However, anticholinergics are not needed and may be detrimental to dogs in 3° AV block. Moreover, dogs with SSS may develop supraventricular tachycardia in response to anticholinergics that preclude postimplantation pacemaker testing. This problem can be overcome by causing the heart rate to slow (e.g., deepening anesthesia) or by programming the pacemaker at a rate that will be overridden by the inherent rate. Premedication that allows the placement of a temporary pacemaker before anesthesia induction may be desired because it is usually not possible to perform this procedure in the awake animal. Another important consideration is postoperative tranquilization. It is ideal to restrict excitement and movement of the animal during the first 24 hours after surgery in hopes of lessening the opportunity for lead dislodgment.

PACEMAKER IMPLANTATION PROCEDURES

A variety of approaches and pacing techniques have been described involving endocardial or epicardial lead placement.[1–9, 43–45] Regardless of the type of pacing selected, a temporary pacemaker may be placed either in all animals or only in those at high risk (Table 20–1). Once the permanent pacemaker is implanted, the temporary pacemaker is turned off to avoid competitive rhythms (Fig. 20–12). Whether or not a temporary pacemaker is used, isoproterenol (0.01 μg/kg/min) should be available so that an infusion can be started if the escape rhythm fails to rescue the heart. For both temporary and permanent endocardial pacemaker implantation, fluoroscopy is required. However, the location of the pacing lead for temporary pacing can be guided by intracardiac electrocardiography (Fig. 20–13).

Endocardial pacing involves placement of the lead down the jugular vein, and the pulse generator is

TABLE 20–1
Temporary Pacemaker Implantation*

Equipment and Supplies
1. Arrow Percutaneous Sheath Introducer Set (18-Ga needle, 18-Ga catheter with stylet, guidewire, dilator, introducer), syringes with heparinized saline
2. Pacing lead (variable, can be quadripolar electrophysiologic catheter, etc.); No. 5 French most common size
3. Temporary pacemaker

Procedure†
1. With the dog in right lateral recumbency, the left groin is surgically prepped and draped.
2. The left femoral artery is palpated as the caudal landmark for the femoral vein.
3. A small incision (2-mm) is made in the skin above the femoral vein, 1 to 3 mm from the femoral artery.
4. At a 30 to 45° angle to the skin, a needle or catheter (with stylet) connected to a syringe with heparinized saline is slowly advanced with the bevel down. Negative pressure is held on the syringe as the needle or catheter is advanced so that blood is aspirated as the vein is entered.
5. Once blood is seen, the syringe or syringe and stylet are removed while securely holding the needle or catheter.
6. A guidewire is threaded through the needle or catheter until it is located well within the vein (e.g., 3 to 5 cm).
7. The needle or catheter is backed out of the vein, slipped back over the guidewire, and removed.
8. The dilator and introducer are slipped over the guidewire and with a gentle, twisting motion are advanced through the vein.
9. At the time that the introducer meets the entry point to the vein, a more forceful, yet still gentle, push is usually required.
10. The dilator is removed, leaving the introducer in place, and the system is flushed with heparinized saline.
11. A pacing lead is advanced, preferably with fluoroscopic guidance, to the right ventricular apex.
12. The pacing lead is connected to the temporary pacemaker.
13. The temporary pacemaker is programmed for a heart rate that will improve the cardiovascular status but not be excessively high. If the rate is too rapid and lead dislodgment results in a loss of capture, overdrive stimulation can suppress subsidiary pacemakers. Therefore, the rate is usually set for 60 to 80 beats/min. The voltage output is usually programmed for 1.5 to 2 V. The temporary pacemaker is not put in asynchronous mode, but the sensitivity is adjusted to sense inherent rhythms.

*Temporary pacing may also be done via the jugular vein. We prefer the femoral vein because it allows for better sterility and better manipulation of the pacing lead (temporary leads in the jugular vein are on the downside of the dog as the permanent lead is placed in the contralateral, "up" jugular vein; this can be awkward during emergency situations). Moreover, should the jugular vein selected for permanent implantation be defective or damaged, preservation of the other jugular vein is an advantage.

†When it is known that a pacemaker will be implanted, the jugular veins should not be used for blood collection so that they are available and undamaged for transvenous pacemaker lead implantation.

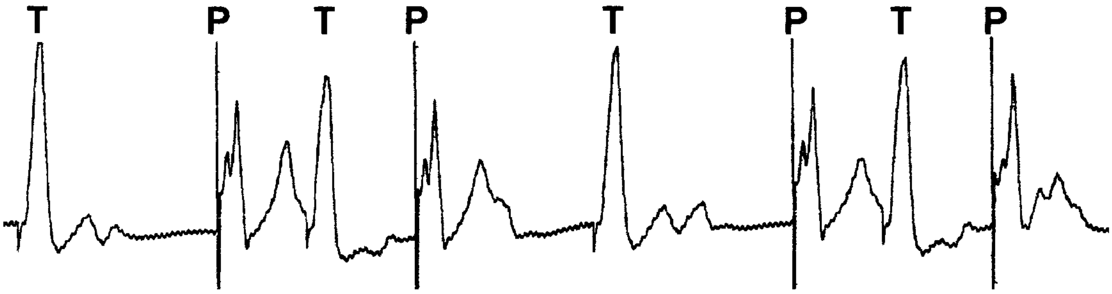


FIGURE 20–12

Electrocardiogram from a dog during pacemaker implantation. The temporary pacemaker *(T)* should be turned off immediately after permanent pacing *(P)* begins to avoid competitive rhythms. Neither pacemaker is sensing properly. Paper speed, 25 mm/sec. 1 mV = 1 cm.

usually positioned on the lateral aspect of the neck (Table 20–2) (occasionally the generator is placed over the cranial lateral thorax after tunneling the lead from the jugular vein access). Lead dislodgment is the most common complication of pacemaker implantation and occurs most often in larger dogs. Movement of the neck may contribute to this particular complication. Therefore, an alternative method for lead and generator placement can be used in patients prone to lead dislodgment (Table 20–3). This procedure uses the costocervical vein for venous access (Fig. 20–14). The costocervical approach does have the major disadvantage that it requires a thoracotomy and fluoroscopy. However, in those frustrating cases of lead dislodgment, this procedure works.

Atrial pacing may be the ideal mode of pacing in

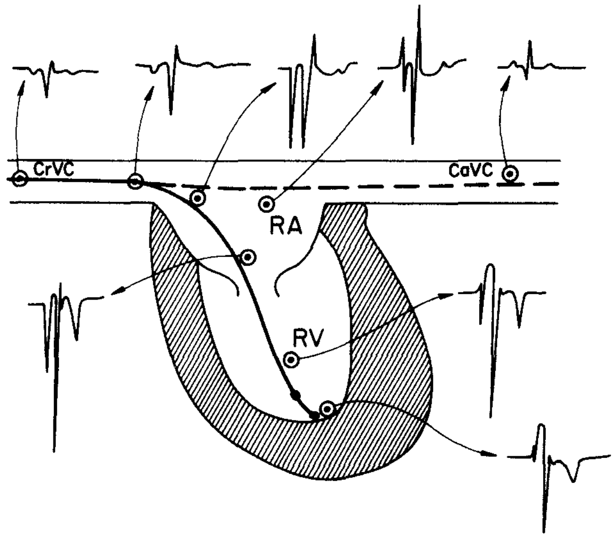


FIGURE 20–13

Intracardiovascular ECG complexes that correspond to various sequential placements of an electrophysiologic catheter (corresponding recording positions are indicated by *arrows* to each representative P-QRS-T complex. From left to right: the catheter was advanced from the cranial vena cava (CrVC), into the right atrium (RA), through the tricuspid valve, and finally into the right ventricle (RV). Also shown is the electrogram when the lead is passed into the caudal vena cava (CaVC).

dogs with sick sinus syndrome (Table 20–4). In the majority of cases, endocardial pacing is the preferred method; however, in very small animals or when venous access is not possible, epicardial pacing may be required (Table 20–5). Epicardial pacing is most commonly performed by a transdiaphragmatic technique,[43–45] although a thoracic approach can be used when necessary.

COMPLICATIONS OF PACING

Complications involving pacemaker therapy have been described in humans and animals.[1–9, 46, 47] Attention to detail before, during, and after implantation can help reduce the probability of most complications. However, owing to the technical difficulties of pacemaker implantation, the intricacy of pacing systems, and the complexities involved in successful pacing, certain complications are inevitable in a small percentage of cases.

LEAD DISLODGMENT

The most common complication of transvenous pacemaker therapy is lead dislodgment or malposition.[7, 24] This usually occurs within the first few days or weeks following implantation. Dislodgment may be characterized by marked estrangement of the pacing lead from its ventricular pacing site, or it may appear subtle, with the lead just missing contact with the endocardium. All types of leads can become dislodged. Causes include (1) improper screwing of an active fixation lead, (2) improper lodging of the tined lead in the RV trabeculae, (3) excessive neck motion in the postoperative period, (4) too little or too much slack in the lead, and (5) excessive movement of the pulse generator. Pulse generator movement can be lessened with the use of a Parsonsett pouch.[8]

Lead dislodgment can be suspected from the history,

TABLE 20-2
Transvenous Endocardial Ventricular Pacemaker Implantation via the Jugular Vein

Equipment and Supplies
1. Fluoroscope, defibrillator, ECG machine with oscilloscope, oxygen saturation monitor, Doppler blood pressure instrument, pacing system analyzer (PSA), emergency crash cart
2. Sterile surgical pack [curved hemostats; straight, smooth hemostat; needle holders; towel clamps; scalpel handle, scalpel blades (#10, #11); Adson tissue forceps, Metzenbaum scissors, Mayo operating scissors, iris scissors, suture scissors; vein pick; 2-0 or 3-0 silk suture, 2-0 or 3-0 absorbable monofilament suture]
3. Pacemaker and lead (including curved and straight stylets) for implantation
4. Spare pacemaker and lead
5. Polyester Parsonnet pouch if animal has very little subcutaneous tissue
6. Adapter sleeves to couple mismatched pacing lead and pulse generator
7. Hex wrench tool, fixation tool, and stylet guide
8. Intravenous antibiotics (usually cephalosporin)—optional

Prepacemaker Implantation Readiness
1. Read manufacturer's instructions for the pulse generator and lead.
2. Note and record the preprogrammed values for the pacemaker. These may be the nominal settings made at the factory or represent settings that have been reprogrammed elsewhere. If a programmer is available, initial values can be reprogrammed for optimal performance when necessary.
3. To help prevent the lead advancement into the caudal vena cava, a curve is imparted to one stylet by grasping the stylet approximately 5 cm from the tip, and with the other hand, pressing a smooth hard object against the wire as the object is pulled toward the tip (as in making ribbon). Pulling the wire between the thumb and index finger also can make this arch. The curve should match the arch taken to enter the right ventricle.
4. When using an active fixation (e.g., screw-in, helix electrode) pacemaker lead, the mechanical function should be verified before implantation. Within the sterile field, a straight stylet is inserted into the lead. Using the fixation tool (Fig. 20–7), the connector pin of the lead is grasped with the most distal hole. The tool is rotated clockwise until the coiled electrode is completely exposed (1.5 to 2 coils). Excessive rotations will damage the lead. The maximum number of rotations is stated in the instructions for each lead. A J-shaped stylet (atrial lead) will require more rotations. The fixation tool is disconnected from the connector pin, and the lead is released. This allows any residual torque in the lead to be relieved. After this test, the fixation tool is again attached, and counterclockwise motion retracts the coil into the protective sheath.

Pacemaker Implantation Procedure
1. Position the animal in left lateral recumbency and place a rolled towel under the neck. Position the head so that the jugular vein is easily seen and the skin of the neck is mildly taut.
2. Surgically prep and drape the cervical region, allowing enough room for the pulse generator pocket (the prepped area should be generous).
3. At the base of the neck, make a 5- to 8-cm-long incision slightly dorsal to the distended jugular vein.*
4. Bluntly dissect the subcutaneous tissue. Expose and free up approximately 3 to 4 cm of the jugular vein.
5. Using the curved hemostats, slip two strands of moistened silk suture under the jugular vein so that the cranial and caudal loop can be grasped to raise the vein manually from the surrounding structures. The cranial ligature is tied, and the caudal ligature is held somewhat taut to allow blood to enter and distend the vein, while controlling hemorrhage.
6. With smooth, straight hemostats, a portion (one third to one half of the diameter) of the vein is pinched perpendicular to its long axis. This action causes a tenting of the vein along its long axis.
7. A #11 blade or iris scissors is used to perform a horizontal venotomy. The incision must be deep enough to reach the lumen but not deep enough to sever the vein.
8. A soft, curved stylet is inserted into the lumen of the lead.
9. The lead and stylet are advanced through the venotomy into the central venous circulation. This can be aided by using a vein pick.
10. Under fluoroscopic guidance, the lead is guided into the right ventricle. Once the lead is positioned in the middle of the RV, the curved stylet is exchanged for a straight stylet to facilitate lead placement in the RV apex.
11. The fixation tool is positioned on the connector pin (see earlier), and the lead tip with the straight stylet is gently pressed against the endocardium. The tool is rotated clockwise. When the coil is completely extruded, this torque is released. Complete coil extraction is verified by fluoroscopy. Two radiopaque crimp sleeves are separated when the coil is fully retracted, and this appearance should be noted during the initial fluoroscopic examination. With full extension of the coil, the crimp sleeves come together.
12. The whole lead is rotated approximately 1 revolution clockwise to ensure that the helical electrode is secured to the endocardium.
13. The stylet is then carefully withdrawn.
14. Ideally, a pacemaker system analyzer (PSA) is used to obtain initial thresholds. A pulse duration of 0.5 ms is used. The maximum acute amplitude should be 1.0 V with a resistance of 300–1200 ohms. The minimum acute sensing amplitude should be 5.0 mV. Values will vary depending on the lead type and cardiac tissue condition. If acceptable values are not initially found, wait 10 minutes and repeat. If thresholds are still too high, lead repositioning is required.
15. An electrogram is recorded from the implanted lead (through the notch of the stylet guide) to identify the current of injury (i.e., ST segment elevation). Such an appearance indicates good contact.
16. A "tug test" is performed with the stylet in place. The lead is gently tugged while observing the heart with fluoroscopy. Resistance is felt when the lead is secured properly. Also, the lead will move with the heart as the heart shifts with each contraction. If not secure, retract the coil and begin again.
17. The stylet is removed and the connector pin is inserted into the pulse generator. Care should be taken to push the pin completely into the connecting port. Visually inspect this system to observe that the end of the lead is appropriately seated in the pulse generator.
18. A hex wrench tool is inserted through the rubber slit of the grommet to engage the setscrew in the connector block. To secure the lead, turn the hex wrench tool clockwise until resistance is felt. Do not overtighten the setscrew.
19. If the pulse generator is a bipolar system, pacing will begin. If the pulse generator is a unipolar system, pacing will begin when the uninsulated side of the pulse generator is placed in contact with the tissue.
20. Once pacing begins, the temporary pacemaker should be turned off to avoid complications (see Fig. 20–12).
21. A subcutaneous pocket is prepared by digital dissection. The size of the pocket should be minimal so that it will snugly accommodate the pulse generator and any residual lead. A small amount of lead slack is allowed, with a bit extra pushed into the vein. The residual lead is loosely wrapped in a circle (*not* in a figure 8, not coiled, not around the generator, and not tightly) (see Fig. 20–19). It is then placed under the pulse generator.
22. The pulse generator is attached to adjacent tissues by placing a nonabsorbable suture through the suture hole located in the pulse generator connector assembly.

TABLE 20-2
Transvenous Endocardial Ventricular Pacemaker Implantation via the Jugular Vein *Continued*

Pacemaker Implantation Procedure *Continued*

23. The lead is secured in the vein with the aid of a grooved anchoring sleeve that fits over the lead (see Fig. 20–7). The sleeve is pushed caudally down the lead until it enters the vein. At this point, sutures are placed around the sleeve and fascia and tightened securely. Manufacturers highly recommend that the sutures not be placed directly around the bare lead itself.
24. The pulse generator pocket is carefully sutured closed, taking care to eliminate dead space, which helps prevent seroma formation and pulse generator motion.
25. The subcutaneous tissues and skin are closed routinely.

*An alternative to the jugular vein cutdown approach (described in steps 3 to 7) is a percutaneous jugular vein catheterization technique. By this method, a 9 French, 15.5 cm long sheath (Peel-Away Introducer Set, Type C-PLI, Cook, Bloomington, IN) is introduced through the skin into the jugular vein, through which the pacemaker wire is inserted. The sheath is then peeled away, leaving the pacing lead in place. The proximal pacing lead is then tunneled subcutaneously to the pacemaker pocket and attached to the pulse generator.

Postpacemaker Implantation Medical Record Notations and Procedures

1. Important data to record in the medical record include:
   a. The pacemaker manufacturer, model and serial number, and radiopaque ID code
   b. The type of lead (active, passive, steroid or nonsteroid-eluding), manufacturer, model and serial number. This information is valuable should the pulse generator require replacement.
   c. Note whether or not an upsizing or downsizing sleeve was used.
   d. All threshold values
   e. All programmed values
2. Perform a 12-lead ECG for future comparison of P-QRS-T morphology.
3. Take lateral and dorsoventral (or ventrodorsal) thoracic radiographs; include the neck to visualize the pulse generator.
4. General home care instructions for the owner:
   a. Monitor heart rate daily for 8 weeks; then weekly.
   b. Call if the heart rate slows more than 5 beats from the original heart rate.
   c. Call if any infection or seroma develops.
   d. Sutures should be removed and the bandage rechecked in 10–14 days.
   e. Recheck to evaluate pacing thresholds at 8 weeks post-op.
   f. Recheck every 6 to 12 months (or as dictated by the animal's cardiac status) after 8-week follow-up.
5. During each visit, the pacemaker ideally should be interrogated with a programmer.

ECG, and pacemaker interrogation. Clinical signs such as weakness or syncope usually recur within days or a few weeks of pacemaker implantation. The ECG often reveals complete or intermittent loss of pacing (i.e., loss of capture). The initial bradyarrhythmia is usually present on the ECG. Moreover, there is loss of sensing as evidenced by the presence of pacing artifacts but without associated QRS complexes (Fig. 20–15). Continuous ECG (Holter) recordings may be required to identify intermittent loss of capture.

When evaluating an ECG from an animal with suspected pacing malfunction, careful examination of multiple leads may be required to identify the pacing spike. This is especially true when examining Holter recordings that may filter out the high-frequency spikes to such a degree that unipolar spikes are greatly attenuated and bipolar spikes are not visible. If the ECG records a change in QRS morphology of the paced beats compared with the morphology at the time of implantation, one should suspect incipient lead dislodgment. Interrogation of the pacemaker will reveal high-voltage threshold and normal lead impedance when lead dislodgment is present. Modern ECG machines have internal filters that usually cause high-

TABLE 20-3
Transvenous Endocardial Ventricular Pacemaker Implantation via the Right Costocervical Vein*

Equipment

1. Thoracic surgical pack (including rib retractors, tunneling device, Rumel's tourniquet)
2. Ability to provide patient ventilation

Procedure

1. Perform thoracotomy through the right second intercostal space.
2. Isolate the costocervical vein (CCV) (see Fig. 20–14) from the mediastinal pleura and ligate it (2-0 silk) 3 cm distal to the vena cava.
3. Temporarily occlude the CCV, using a Rumel's tourniquet placed at the junction of the CCV and the cranial vena cava.
4. Make a venotomy incision between the ligature and the tourniquet; advance the lead into the central venous circulation as the Rumel's tourniquet is loosened.
5. Using fluoroscopy, position the lead in the right ventricular apex.
6. Make a 5-cm vertical incision over the right 7th rib. Create a small pocket deep to the external abdominal oblique muscle caudal to the 7th rib.
7. Tunnel the lead deep to the subcutaneous tissues of the lateral thorax. The lead should exit from the incision over the 7th rib.
8. The lead connections and pulse generator placement are performed as described in Table 20–2.

*Only the procedural steps that are relative to lead placement in the costocervical vein are listed in this table. For more complete implantation details, see Table 20–2.

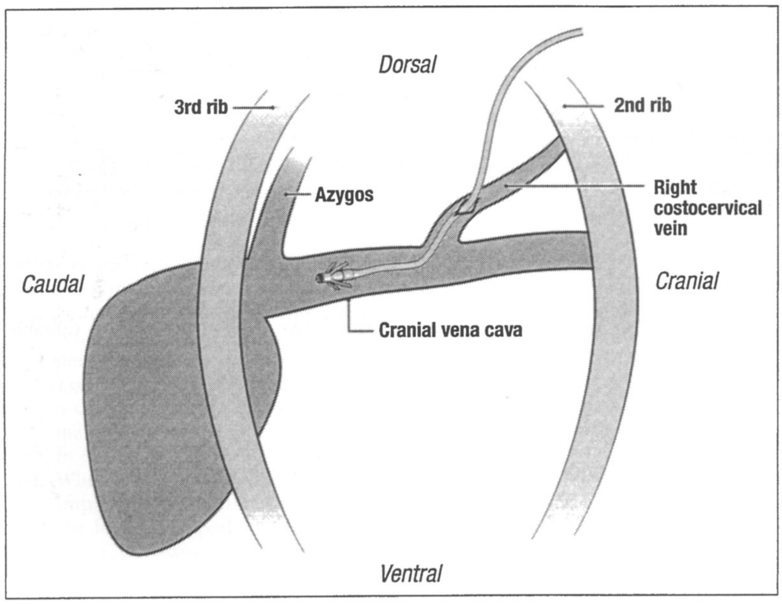


FIGURE 20–14

The anatomic location of the right costocervical vein.

TABLE 20–4
Transvenous Right Atrial Endocardial Pacemaker Implantation via the Jugular Vein*

Steps	Using a Straight Screw-in Endocardial Pacemaker Lead	Using an Atrial J-shaped Screw-in Endocardial Pacemaker Lead
1	Insert a straight stylet into a straight screw-in endocardial lead. Using fluoroscopic guidance, advance the lead tip into the right atrium (RA).	Insert a straight stylet into an atrial J-shaped screw-in lead. Using fluoroscopic guidance, advance the lead tip into the right atrium (RA).
2	Once the lead tip is positioned within the RA, the straight stylet is withdrawn from the lead and is then replaced by a J-shaped stylet.	Once the lead tip is positioned within the RA, the straight stylet is partially withdrawn from the lead. This allows the lead to assume its preformed J-shape.
3	Position the pacemaker lead tip so that the curve is directed cranially toward the right auricle.†	Position the pacemaker lead tip so that the curve is directed cranially toward the right auricle.†
4	Secure the lead tip into the right auricle by gently pressing the tip into myocardium and rotating the fixation tool (see Table 20–2). *Note*—atrial lead securement usually requires several rotations with the fixation tool.‡	Completely withdraw the straight stylet from the lead while maintaining gentle retraction on the lead (this retraction secures the lead against the auricular endocardium). Insert the J-shaped stylet into the lead. Secure the lead by rotating the fixation tool (see Table 20–2). *Note*—atrial lead securement usually requires several rotations with the fixation tool.‡
5	Atrial lead thresholds at implantation are: Max. Stimulation amplitude, 1.5 V; Resistance, 300–1200 ohms; Sensitivity, 2 mV	Atrial lead thresholds at implantation are: Max. Stimulation amplitude 1.5 V; Resistance, 300–1200 ohms; Sensitivity, 2 mV

*Only those details relating to atrial lead placement are contained here. Refer to Table 20–2 for a more complete description of transvenous endocardial pacemaker lead implantation.

†The position of the lead tip is judged to be satisfactory when the lead tip moves in a dorsoventral plane in concert with the beating heart.

‡Atrial lead securement is assessed by gently inserting additional lead "slack" into the right atrium. The lead tip must remain stable to insure that it is lodged in the atrial appendage (Fig. 20–2).

TABLE 20-5
Epicardial Ventricular Pacemaker Implantation*

Equipment
1. General surgical pack
2. Epicardial pacing lead (usually, a screw-in lead)
3. Tunneling tool
4. Ability to perform patient ventilation
5. Epicardial pacing lead

Procedure
1. Position the animal in dorsal recumbency, with the legs pulled cranially.
2. Surgically prep and drape the ventral abdomen and the caudal ventral thorax.
3. Perform a midline celiotomy, beginning just cranial to the xiphoid, and extend the incision just caudal to the umbilicus.
4. Use Balfour's retractors to expose the diaphragm while gently retracting the liver caudally.
5. Incise the diaphragm left of the midline to expose the cardiac apex.
6. Begin ventilating the patient.
7. Place stay sutures along the edge of the diaphragmatic incision.
8. Grasp the pericardium with DeBakey's forceps, tent it away from the heart, and incise the pericardium with small scissors.
9. Place stay sutures in the pericardium to lift the heart so that the apex is exposed.
10. Twist a corkscrew epicardial lead into the epimyocardium (avoid coronary vessels), using the specific plastic instrument designed for this purpose. Leave the pericardium open.
11. Connect the lead as described in Table 20-2.
12. Remove stay sutures; close the diaphragm with the pacing lead exiting from the incision (leave a tension-relieving loop on the thoracic side of the diaphragm).
13. Create a pocket between the transverse muscle of the abdomen and the internal abdominal oblique muscles.
14. Close the abdominal wall routinely.

*This table describes the particular features for placement of an epicardial lead. Only those aspects that differ from those described for placement of the lead via the jugular vein are described here. See Table 20-2 for more complete details.

frequency pacing spikes to be recorded with varying amplitudes (Fig. 20-16). This does not indicate pacemaker malfunction.

Radiography, fluoroscopy, and echocardiography can confirm the diagnosis of lead dislodgment. Radiographs taken immediately after implantation are compared with those taken at the time of the loss of capture, sensing, or both (Fig. 20-17). It is always best to expose two radiographic views. Lead dislodgment is usually apparent, but subtle changes in position can make the diagnosis more difficult. If there is a question as to the location of the lead, fluoroscopy can be used to identify lead motion with each heartbeat. Frequently, the lead dislodgment can be identified by echocardiography, especially for atrial lead dislodgment.

Once lead dislodgment is diagnosed, treatment requires a second procedure to reposition the existing lead more optimally or to replace the original pacing system. Ideally, the cause of the dislodgment should be identified to avoid repeating the mistake or to lessen the chance of it recurring. Most often the same lead can be reused and properly repositioned, although a clot or fibrosis on the lead tip may hinder proper function. At the time of surgery a second complete pulse generator and pacing lead should be available in case problems are encountered with the original system.

PACEMAKER NOT PACING AS PROGRAMMED

Occasionally, a pacemaker will not pace the heart in accordance with the programmed rate and parameters (Fig. 20-18).[18, 24, 25] Careful interrogation of the pulse generator should then be made. Reasons for this include (1) battery depletion, (2) sticking reed switch (places the pulse generator into magnet mode), (3) defibrillation, and (4) inadvertent reprogramming. A problem encountered in cold climates is the resetting of the pulse generator in response to cold (Fig. 20-18). Pulse generators shipped during the winter that do not pace at the rates programmed but instead pace at a slower rate should be suspected to have been affected by cold temperature. This causes battery voltage to drop, but the programmer can be used to reset the pacemaker to normal function.[25]

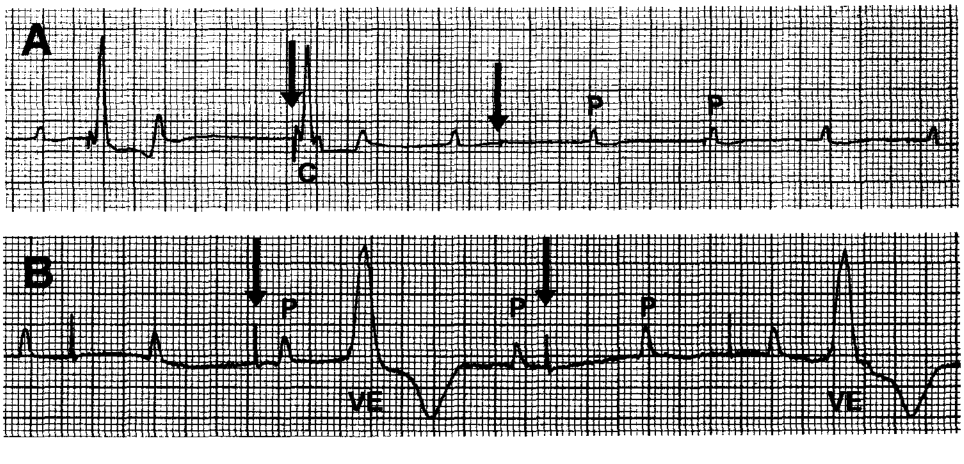


FIGURE 20-15

(A) ECG recorded from a dog with 3° AV block and pacemaker malfunction. Pacemaker capture is intermittent. There are pacing artifact spikes that precede capture *(C), first arrow,* and pacing artifact spikes *(second arrow)* without ventricular capture (i.e., absent QRS-T complexes). *P,* P waves. The pulse generator power source in (A) was depleted. The dog in (B) had pacemaker lead dislodgment. See text for complete differential diagnosis. Paper speed, 50 mm/sec. 1 mV = 1 cm.

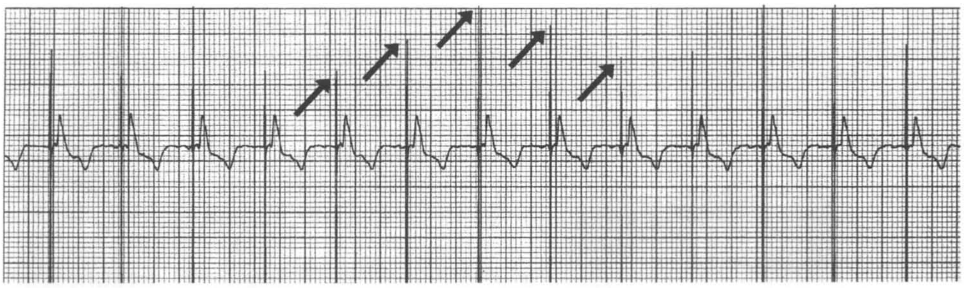


FIGURE 20–16

Electrocardiogram recorded from a dog using a digital electrocardiograph. Such recordings usually show variation in the amplitude of the pacing spike *(arrows)*. This is a function of the frequency of the recording and the high frequency of the spike. It does not indicate a pulse generator abnormality.

LOSS OF CAPTURE WITH NO PACING SPIKES

Careful examination of multiple ECG leads can help determine whether lack of pacemaker capture is associated with loss of the pulse generator pacing stimulus. One must be mindful that bipolar pacing systems and excessive filtering inherent in digital electrocardiograph machines can reduce the size of the pacing artifact to the point that it is difficult to visualize.[25] True loss of pacemaker capture can be continuous or intermittent. Reasons for this complication include (1) battery failure,[1, 45] (2) circuit failure, (3) lead fracture (Fig. 20–19), (4) unipolar lead wrongly placed in a bipolar device, (5) incompatible connection between lead and pulse generator, (6) oversensing (see later), (7) unipolar pulse generator not in contact with tissue, (8) "cross-talk" in a dual-chamber device, (9) loose connection (setscrew not secured, improper pin insertion) (Fig. 20–20), and (10) insulation failure.

LOSS OF CAPTURE WITH PACING SPIKES

The presence of pacing spikes, but a failure to capture and pace, is most commonly caused by lead dislodgment (see Fig. 20–15). Other causes include (1) inadequate stimulus (voltage, pulse width), (2) exit block,[47] (3) inappropriate lead placement (e.g., in the vena cava), (4) lead fracture, (5) improper contact (setscrew not secured, improper pin insertion), (6) battery failure, (7) insulation failure, (8) circuit failure, (9) certain drug therapy, (10) lead perforation, or (11) metabolic factors (e.g., severe hyperkalemia).[25] Holter monitoring may be needed to detect losses of capture that may correspond to inadequate stimulus. This is because thresholds do change during the day and during certain activities.

When the pacing threshold increases over time until capture is no longer occurring, exit block should be

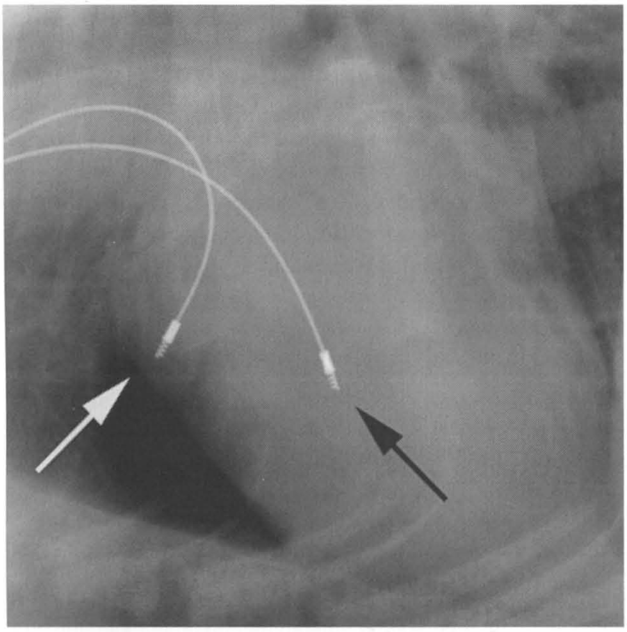


FIGURE 20–17

Right lateral thoracic radiograph of a dog with a dual chamber pacemaker. Although the right atrium was pacing *(white arrow)*, the ventricle was not. The ventricular lead is dislodged *(black arrow)* from its initial, correct, right ventricular apical position.

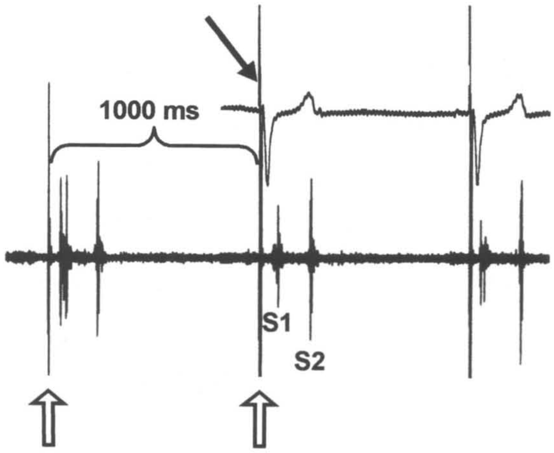
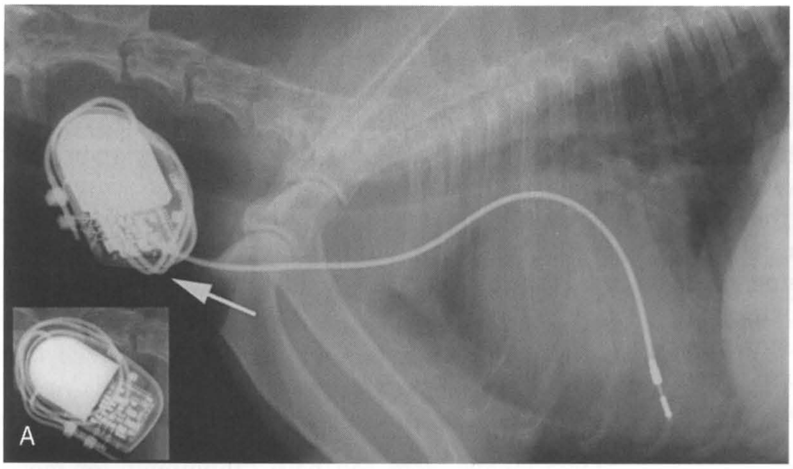


FIGURE 20–18

Electrocardiogram *(top trace)* recorded from a dog with a pacemaker that was not pacing at the programmed rate. The pulse generator was shipped during the winter and was exposed to temperatures lower than −10° C. The pulse generator was reset and reprogrammed. The black arrow indicates the pacing artifact spike of the unipolar pulse generator. A presystolic click was auscultated. Phonocardiography *(bottom trace)* revealed that this was caused by the pacemaker (*open arrows* point to the presystolic click—compare the timing of the 2nd open arrow to the pacemaker spike above). This observation is described in humans as well. The first *(S1)* and second *(S2)* heart sounds are indicated. Paper speed, 50 mm/sec. 1 mV = 1 cm.



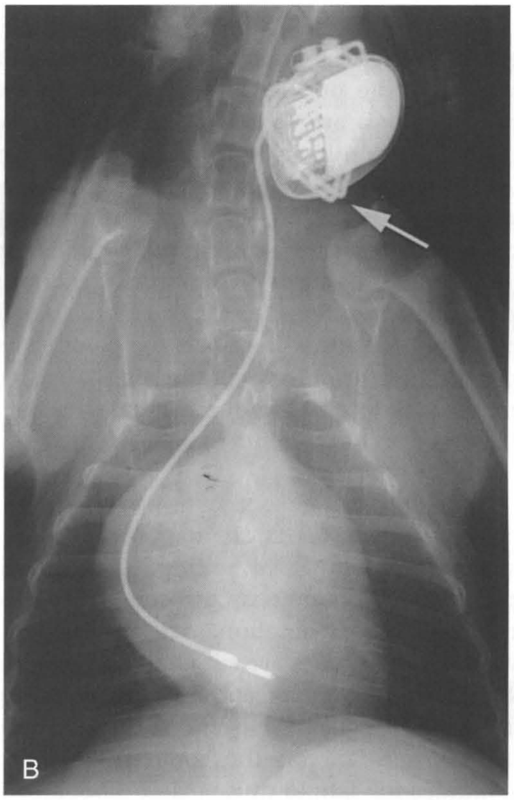


FIGURE 20–19

(A) Right lateral and (B) dorsoventral radiographs show an endocardial pacemaker lead that has been wrapped too tightly around the pulse generator. Notice that the circular loops of pacemaker lead are bent at an inappropriately acute sharp angle *(arrows)*. The inset in (A) shows how the pacemaker lead should be properly wrapped to avoid lead kinking or bending and should be placed underneath the pulse generator.

excluded. Exit block, which is uncommon, is caused by fibrous tissue at the electrode-myocardium interface.[48] There is no change in the morphology of the QRS with exit block because the lead has not moved. Increasing the voltage and pulse width may temporarily relieve the problem; however, repositioning the lead usually is necessary. Treatment with systemic steroids may have some beneficial effects. This observation led to the use of steroid-eluding leads, which have essentially eliminated this problem.[49] Permanent elevations in capture thresholds that do not respond to steroids can develop with progressive myocardial fibrosis due to a primary myopathic process (see Fig. 20–10).[20]

IMPROPER SENSING

OVERSENSING. This occurs when an inappropriate signal is sensed,[25] and it is characterized by a loss of capture without a pacing spike on the ECG. Oversensing can be differentiated from other causes of loss of capture by placing the programming head in the

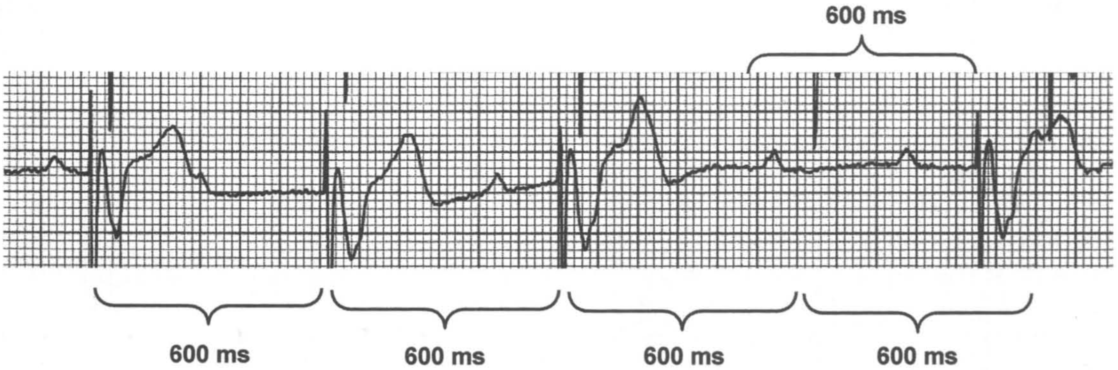


FIGURE 20–20

An epicardial pacemaker was failing to pace properly. Although the rate was programmed at 100 beats/min, pacing was not constant. A loss of capture without the pacing artifact was documented. Oversensing was not the problem because the intervals did not match up, and when the pulse generator was switched to "magnet mode," the loss of capture continued. In this case, failure to pace properly was attributed to a loose setscrew that permitted the pacemaker lead to fit loosely, move, and lose contact within the pulse generator. Paper speed, 50 mm/sec. 1 mV = 1 cm.

magnet mode and positioning it over the pulse generator. If pacing resumes and pauses are eliminated, oversensing is the problem. Oversensing can occur when myopotentials are sensed primarily with unipolar systems. If the sensitivity is programmed too high (numerical number too low), oversensing of the P waves or T waves can occur. To correct the problem, the pacemaker setting is reprogrammed to be less sensitive.

Afterpotentials can be a source of oversensing, especially if the pacing stimulus is of high amplitude and duration. An afterpotential is the electrical signal produced after the delivery of the stimulation pulse. Afterpotentials are usually not sensed as they fall within the blanking period.[21]

UNDERSENSING. This occurs when the pulse generator delivers a stimulus at an inappropriate time.[21, 25] Observing the timing of pacing spikes relative to the paced and spontaneous QRS complexes is required to make this determination. *Fusion complexes* can occur when the ventricles are stimulated simultaneously by a spontaneous depolarization and a paced impulse (Fig. 20–21).[19] *Pseudofusion* occurs when the pacing spike is superimposed on the spontaneous QRS complex (stimulus too late to cause true fusion, and stimulation occurs during the refractory period of the ventricle) (Fig. 20–21). Sufficient amplitude of the ventricular complex must be achieved in order for the pulse generator to sense the depolarization. The surface ECG may reach sufficient voltage amplitude to be seen before the intracardiac electrogram has reached the sensing amplitude (recorded under the electrode). This is the cause of pseudofusion complexes. Pseudofusion complexes may be confused for undersensing, but if the pacing spike falls after the termination of the surface QRS complex, then undersensing does exist.[19] Causes for undersensing include (1) improper programming (sensitivity too high), (2) lead dislodgment, (3) lead malpositioning, (4) battery failure, (5) magnet application (see Fig. 20–8), (6) sticking reed switch (places pulse generator in fixed [asynchronous] pacing mode), (7) poor slew rate, and (8) intrinsic beat falling in the device's refractory period (see Fig. 20–4). With dual pacing systems, cross-talk inhibition can occur. Cross-talk inhibition causes ventricular oversensing of atrial depolarizations, thus inhibiting ventricular pacing. Confusing patterns of improper sensing can be recorded during the transition of temporary to permanent pacing during the implantation procedure (see Fig. 20–12).

EXTRACARDIAC STIMULATION

Occasionally, dogs will have "thumping" or movement of their neck or diaphragm with each pacing stimulus. The most common reason for this is a unipolar device programmed with a high output. If the pacing threshold is determined, the voltage usually can be lowered and still fall well within the safety margin for capture. Other reasons for extracardiac stimulation include (1) close proximity of the electrode to the diaphragm, (2) phrenic nerve stimulation, (3) lead insulation failure, (4) device placed upside down, or (5) lead perforating the heart.[25]

DEVELOPMENT OF CONGESTIVE HEART FAILURE

Some dogs develop CHF after pacemaker implantation. We have observed this phenomenon in dogs with acquired 3° AV block and with SSS. Dogs with 3° AV block most commonly develop CHF secondary to myocardial failure (see Fig. 20–10). Critical review of preoperative echocardiographic indices of myocardial structure and function is therefore important to detect dogs that may have marginally normal contractility. A dog with good function should have a fractional shortening that is above normal (chapter 8); other-

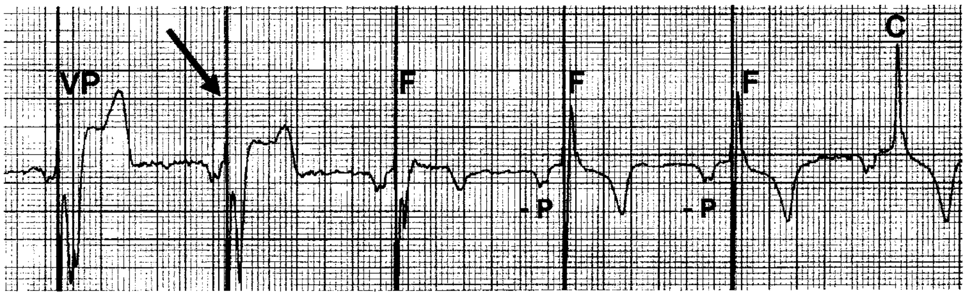


FIGURE 20–21

Electrocardiogram recorded from a dog with sick sinus syndrome. The unipolar pacemaker (*arrow* indicates artifact spike) is pacing the ventricle, but fusion beats *(F)* are occurring (the inherent rate and the pacing rate are similar). If the pacing spike were delayed just slightly more in the last fusion beat, a "pseudofusion" would have occurred. (See text for explanation.) A spontaneous complex (C) follows one of the negative P waves. Paper speed, 50 mm/sec. 1 mV = 1 cm.

wise, careful follow-up for this complication is warranted.

The cause of myocardial failure observed in this small subset of dogs is unknown. One possibility is that the disease process that caused heart block was also associated with incipient, progressive myocardial failure (cardiomyopathy). Alternatively, long-term and marked bradycardia could have resulted in irreversible myocardial damage. Finally, pacemaker syndrome (see next) could play a primary or contributory role. Dogs with SSS may occasionally develop CHF, but this is due to chronic, progressive mitral and tricuspid valve degeneration (endocardiosis). However, the fact that VA conduction is likely to be common in these dogs raises the probability that pacemaker syndrome contributes to the failure. Additionally, it is conceivable that VVI (ventricular) pacing could increase the regurgitant fraction across the incompetent valves.

PACEMAKER SYNDROME

Pacemaker syndrome was first described in humans as a complication of ventricular pacing that resulted in CHF.[50, 51] However, pacemaker syndrome can occur with other modes of pacing when the proper timing between atrial contraction and ventricular contraction is absent.[52] Most of the hemodynamic alterations (decreased cardiac output and systemic blood pressure) of pacemaker syndrome result from the loss of AV sequential pacing and ventriculoatrial (VA) conduction (see Fig. 20–9).[53, 54] However, reflexes elicited by increased pulmonary artery and pulmonary venous pressures may contribute to the syndrome.

Clinical evidence of right- or left-sided heart failure that has exacerbated or developed after pacemaker implantation should raise the suspicion of pacemaker syndrome. However, it may be difficult to differentiate the development of failure from progression of an underlying disease and the pacemaker syndrome. A specific diagnosis is reached if the clinical signs of failure resolve or improve with the restoration of AV synchrony. Obviously, because of the limited use of AV sequential pacing in veterinary patients, proof of this complication is lacking.

Careful cardiovascular examination can identify dogs with SSS that may be susceptible to pacemaker syndrome. Dogs are suspect if after pacemaker implantation the systolic pressure during pacing drops, compared with sinus rhythm. In humans, a greater than 20 mmHg pressure drop implies that pacemaker syndrome exists.[50] This determination should be made immediately after the pacemaker is activated and again 30 seconds after pacing. Doppler echocardiography can be used to assess the effect of atrial contraction against a closed AV valve and the effect of ventriculoatrial conduction.[50, 53, 54] Treatment of an animal with pacemaker syndrome would ideally be the implantation of a dual chamber pacemaker that insured AV sequential pacing. In many situations this may not be possible. Theoretically, this problem is more likely to occur in dogs with sick sinus syndrome (SSS). Therefore, if ventricular pacing and VA conduction can be minimized, improvement is expected. With SSS, prolonged periods of asystole result in syncope. Thus, the pacing rate can be programmed to a minimum to prevent prolonged asystole and to allow the normal sinus rate to predominate. Dogs with primarily a continuous bradycardia would not be helped by this method. Also, hysteresis can be programmed to "on." Hysteresis allows ventricular pacing to occur only after a longer pause than the programmed lower rate.[50] Alternatively, antiarrhythmics can be given to decrease VA conduction, or theophylline can be used in an attempt to increase the sinus rate.

ARRHYTHMIAS

Arrhythmias have been reported as a complication in dogs requiring pacemakers.[1] It is possible for the lead to induce arrhythmias, and these can be recorded most commonly during the immediate postoperative period. In other cases, arrhythmias may become more prevalent in conjunction with progressive underlying heart disease. It is our impression that some dogs in 3° AV block may be more prone to ventricular tachyarrhythmias (Fig. 20–22). Dogs with SSS may have supraventricular tachyarrhythmias in addition to the bradycardia. These rhythm disturbances must be treated with the appropriate antiarrhythmic agents when indicated (see chapter 18).

INFECTIONS

Infections caused by contamination of the implant site at the time of surgery are rare. Most commonly, the infection is metastatic, caused by bacteria seeding the pulse generator pocket from a remote site (e.g., cystitis, dermatitis, teeth cleaning). Thus, it is important that a pacemaker or paced animal be treated appropriately and aggressively for any infections. Fortunately, infection of the pulse generator pocket and/or lead is uncommon. However, if it occurs, the offending lead and generator should be removed and replaced by a new system, using the contralateral jugular vein. If this is not possible, then the site should be assessed with a bacterial culture and sensitivity panel, the infected pulse generator pocket flushed and drained, and appropriate antibiotic given. Treatment of infected pulse generator pockets, however, is often unrewarding with the best treatment being a completely new pacing lead and generator.

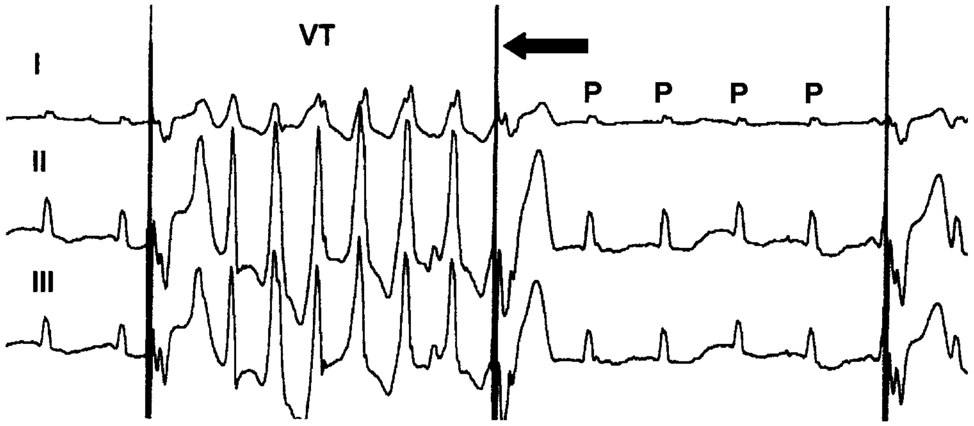


FIGURE 20–22

Simultaneous 3-lead ECG recorded from a boxer with 3° AV block. The pulse generator was at the end of service and the pacing rate was slow. With the slow rate, the dog developed ventricular tachycardia *(VT)*. This resolved once the dog was paced at 90 beats/min. *P*, P wave. *Arrow* indicates the pacing artifact. Paper speed, 50 mm/sec. 1 mV = 1 cm.

SEROMA

A pulse generator pocket seroma is a fairly common and usually minor complication of transvenous pacemaker therapy. Several factors contribute to the development of a seroma: (1) inadequate hemostasis, (2) excessive tissue dissection and trauma, (3) excessively large pocket, facilitating movement of the pulse generator, (4) inadequate closure of tissue layers (promoting pulse generator motion), and (5) pulse generator improperly secured to tissue. To decrease the chance of seroma formation, one must assure proper hemostasis and create a snug fit between the pulse generator and its subcutaneous pocket to avoid motion of the device. In addition, a pressure wrap is applied over the surgical site before the animal is awakened from anesthesia. The bandage is changed every third day for 2 weeks. If a seroma forms, careful fluid drainage by needle centesis, coupled with a snug, soft-padded neck wrap to reduce motion and seroma reformation, is usually successful.

REFERENCES

1. Bonagura JD, Helphrey ML, Muir WW. Complications associated with permanent pacemaker implantation in the dog. J Am Vet Med Assoc 182:149, 1983
2. Buchanan JW, Dear MG, Pyle RL. Medical and pacemaker therapy of complete heart block and congestive heart failure in a dog. J Am Vet Med Assoc 152:1099, 1968
3. Darke PGG, Been M, Marks A. Use of a programmable, "physiological" cardiac pacemaker in a dog with total atrioventricular block (with some comments on complications associated with cardiac pacemakers). J Small Anim Pract 26:295, 1985
4. Darke PGG, McAreavey D, Been M. Transvenous cardiac pacing in 19 dogs and 1 cat. J Small Anim Pract 30:491, 1989
5. Lombard CW, Tilley LP, Yoshioka M. Pacemaker implantation in the dog: survey and literature review. J Am Anim Hosp Assoc 17:751, 1981
6. Musselman EE, Rouse GP, Parker AJ. Permanent pacemaker implantation with transvenous electrode placement in a dog with complete atrioventricular heart block, congestive heart failure, and Stokes-Adams seizures. J Small Anim Pract 17:149, 1976
7. Sisson D, Thomas WP, Woodfield J, et al. Permanent transvenous pacemaker implantation in 40 dogs. J Vet Intern Med 5:322, 1991
8. Fox PR, Moïse NS, Woodfield JA, et al. Techniques and complications of pacemaker implantation in four cats. J Am Vet Med Assoc 199:1742, 1991

8a. Stamoulis ME, Bond BR, Fox PR. Pacemaker therapy for symptomatic bradycardia in the cat. J Vet Emerg Crit Care 2:67, 1992

9. Yoshioka MM, Tilley LP, Harvey HJ, et al. Permanent pacemaker implantation in the dog. J Am Anim Hosp Assoc 17:746, 1981
10. Gregoratos G, Cheitlin MD, Conill A, et al. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: executive summary. Circulation 97:1325, 1998
11. Johnson L, Sisson DD. Atrioventricular block in cats. Comp Cont Educ Pract Vet 15:1356, 1993
12. Michaelsson M, Jonzon A, Riesenfeld T. Isolated congenital complete atrioventricular block in adult life. Circulation 92:442, 1995
13. Liu SK, Tilley LP, Tashjian RJ. Lesions of the conduction system in the cat with cardiomyopathy. Recent Adv Stud Cardiovasc Struct Metab 10:681, 1975
14. Irnich W. The fundamental law of electrostimulation and its application to defibrillation. PACE 13:1433, 1990
15. Kay GN. Basic concepts of pacing. *In* Ellenbogen KA (ed): Practical Cardiac Diagnosis: Cardiac Pacing. Boston, Blackwell Scientific Publications, 1992, p 32
16. Stokes K, Bornzin G. The electrode-biointerface (stimulation). *In* Barold S (ed): Modern Cardiac Pacing. Mt. Kisco, NY, Futura, 1985, p 33
17. Stokes KB, Kay GN. Artificial electric cardiac stimulation. *In* Ellenbogen KA, Kay GN, Wilkoff BL (eds): Clinical Cardiac Pacing. Philadelphia, WB Saunders, 1997, p 3
18. Schoenfeld MH, Padula LE, Harthorne JW. Programmers for cardiac pacemakers. *In* Ellenbogen KA, Kay GN, Wilkoff BL (eds): Clinical Cardiac Pacing. Philadelphia, WB Saunders, 1997, p 127
19. Barold SS, Zipes DP. Cardiac pacemakers and antiarrhythmic devices. *In* Braunwald E (ed): Heart Diseases: A Textbook of Cardiovascular Medicine. Philadelphia, WB Saunders, 1997, p 705
20. Szabo Z, Solti F. The significance of the tissue reaction around the electrode on the late myocardial threshold.

In Schaldach M, Furman S (eds): Advances in Pacemaker Technology. New York, Springer-Verlag, 1975, p 273
21. Kay GN, Ellenbogen KA. Sensing. *In* Ellenbogen KA, Kay GN, Wilkoff BL (eds): Clinical Cardiac Pacing. Philadelphia, WB Saunders, 1997, p 38
22. Belott PH, Reynolds DW. Permanent pacemaker implantation. *In* Ellenbogen KA, Kay GN, Wilkoff BL (eds): Clinical Cardiac Pacing. Philadelphia, WB Saunders, 1992, p 447
23. Wedensky NE. Über die Beziehung zwischen Reizung und Erregung im Tetanus. St. Petersburg, Ber Akad Wiss 54:96, 1887
24. Levine P. Differential diagnosis, evaluation, and management of pacing system malfunction. *In* Ellenbogen KA (ed): Practical Cardiac Diagnosis: Cardiac Pacing. Boston, Blackwell Scientific Publications, 1992, p 309
25. Love CJ, Hayes DL. Evaluation of pacemaker malfunction. *In* Ellenbogen KA, Kay GN, Wilkoff BL (eds): Clinical Cardiac Pacing. Philadelphia, WB Saunders, 1997, p 656
26. Mond HG, Helland JR. Engineering and clinical aspects of pacing leads. *In* Ellenbogen KA, Kay GN, Wilkoff BL (eds): Clinical Cardiac Pacing. Philadelphia, WB Saunders, 1997, p 69
27. Benedek ZM, Gross J. U.S.-available rate modulated pacemakers. Cardiol Pacing Electrophys Spec Ed 11, 1998
28. Benditt DG, Duncan JL. Activity-sensing, rate-adaptive pacemakers. *In* Ellenbogen KA, Kay GN, Wilkoff BL (eds): Clinical Cardiac Pacing. Philadelphia, WB Saunders, 1998, p 167
29. Roberts DH, Tennant B, Brockman D, et al. Successful use of a QT-sensing rate-adaptive pacemaker in a dog. Vet Rec 130:471, 1992
30. Wood M, Ellenbogen KA, Haines D. Temporary cardiac pacing. *In* Ellenbogen KA (ed): Practical Cardiac Diagnosis: Cardiac Pacing. Boston, Blackwell Scientific Publications, 1992, p 162
31. Executive Committee of the German Working Group on Cardiac Pacing: Communication to Professor K. Steinbach, European Working Group on Cardiac Pacing, June 1985
32. Ellenbogen KA, Thames MD, Mohanty PK. New insights into pacemaker syndrome gained from hemodynamic, humoral, and vascular responses during ventriculoatrial pacing. Am J Cardiol 65:33, 1990
33. Mitchell JH, Gupta DN, Payne RM. Influence of atrial systole on effective ventricular stroke volume. Circ Res 17:11, 1965
34. Rosenqvist M, Isaaz K, Botvinick EH, et al. Relative importance of activation sequence compared to atrioventricular synchrony in left ventricular function. Am J Cardiol 67:148, 1991
35. Bishop VS, Haywood JR. Hormonal control of cardiovascular reflexes. *In* Zucker IH, Gilmore JP (eds): Reflex Control of the Circulation. Boca Raton, FL, CRC Press, 1991, p 253
36. Oldroyd RG, Rae AP, Carter R, et al. Double-blind crossover comparison of the effects of dual-chamber pacing (DDD) and ventricular rate-adaptive (VVIR) pacing on neuroendocrine variables, exercise performance, and symptoms in complete heart block. Br Heart J 65:188, 1991
37. Natio M, Dreifus LS, Mardelli TJ, et al. Echocardiographic features of atrioventricular and ventriculoatrial conduction. Am J Cardiol 46:625, 1980
38. Natio M, Dreifus LS, David B, et al. Reevaluation of the role of atrial systole to cardiac hemodynamics: evidence for pulmonary venous regurgitation during abnormal atrioventricular sequencing. Am Heart J 105:295, 1983
39. Ogawa S, Dreifus LS, Shenoy PN, et al. Hemodynamic consequences of atrioventricular and ventriculoatrial pacing. PACE 1:18, 1978
40. Klementowicz P, Ausubel K, Furman S. The dynamic nature of ventriculoatrial conduction. PACE 9:1050, 1986
41. Labovitz AJ, Williams GA, Redd RM, et al. Noninvasive assessment of pacemaker hemodynamics of Doppler echocardiography: importance of left atrial size. J Am Coll Cardiol 6:196, 1985
42. Askenazi J, Alexander JH, Koenigsberg DI, et al. Alteration of left ventricular performance by left bundle branch block simulated with atrioventricular sequential pacing. Am J Cardiol 53:99, 1984
43. Fingeroth JM, Birchard SJ. Transdiaphragmatic approach for permanent cardiac pacemaker implantation in dogs. Vet Surg 15:329, 1986
44. Fingeroth JM. Pacemaker therapy for bradycardias. Semin Vet Med Surg (Small Anim) 9:192, 1994
45. Fox PR, Matthiesen DT, Purse D, et al. Ventral abdominal, transdiaphragmatic approach for implantation of cardiac pacemakers in the dog. J Am Vet Med Assoc 189:1303, 1986
46. Rowland PH, Moïse NS, Severson D. Myxoma at the site of a subcutaneous pacemaker in a dog. J Am Anim Hosp Assoc 27:649, 1991
47. Snyder PS, Atkins CE, Sato T. Syncope in three dogs with cardiac pacemakers. J Am Anim Hosp Assoc 27:611, 1991
48. Fishbein MC, Tan KS, Beaszell JW, et al. Cardiac pathology of transvenous pacemakers in dogs. Am Heart J 93:73, 1977
49. Radovsky AS, Van Vleet JF. Effects of dexamethasone elution on tissue reaction around stimulating electrodes of endocardial pacing leads in dogs. Am Heart J 117:1288, 1989
50. Ellenbogen KA, Stambler BS. Pacemaker syndrome. *In* Ellenbogen KA, Kay GN, Wilkoff BL (eds): Clinical Cardiac Pacing. Philadelphia, WB Saunders, 1997, p 419
51. Hass JM, Strait BG. Pacemaker induced cardiovascular failure: hemodynamic and angiographic observations. Am J Cardiol 33:295, 1974
52. Barold SS. Repetitive reentrant and nonreentrant ventriculoatrial synchrony in dual-chamber pacing. Clin Cardiol 14:754, 1991
53. Goldreyer B, Bigger T. Ventriculoatrial conduction in man. Circulation 41:935, 1970
54. Levy S, Corbelli JL, Labrunie P. Retrograde (ventriculoatrial) conduction. PACE 6:364, 1983

21

Cardiopulmonary and Cerebral Resuscitation

DENNIS T. CROWE, Jr.
PHILIP R. FOX
JENNIFER J. DEVEY
DAVID SPRENG

CARDIOPULMONARY ARREST

Cardiopulmonary arrest (CPA) represents cessation of functional and effective ventilation and circulation. It results from any extreme disease or process that severely disrupts cardiopulmonary function, respiratory gas exchange, or cardiovascular stability. Cardiopulmonary cerebral resuscitation (CPCR) describes life-saving procedures intended to reverse CPA. It is synonymous with cardiopulmonary resuscitation (CPR) but emphasizes brain resuscitation.

Many advances have been made in teaching and practicing CPCR. They emphasize (1) prevention of cardiopulmonary arrest, (2) early recognition, (3) aggressive intervention, (4) improved monitoring, and (5) postresuscitative support. Resuscitation efforts have been temporally categorized into initial *Basic Life Support* procedures to provide **A**—Airway securement, **B**—Breathing, and **C**—Circulation. This is immediately followed by *Advanced Life Support* measures emphasizing **D**—Drug administration and defibrillation, and **E**—Electrocardiographic and other patient monitoring. Prolonged or *Postresuscitative Life Support* includes postresuscitation monitoring and circulatory support.[1]

INCIDENCE

Incidence data are scarce. Cardiopulmonary arrest was represented by 0.46 percent of dogs and cats presenting to a university veterinary teaching hospital,[2] and 1 percent presenting to the author's (DTC) private emergency practice (overall hospital incidence, 3 percent).

OUTCOME

CPR is rarely effective in patients with chronic, debilitating illnesses or acute, multisystemic failure. Although CPR was originally used for victims of acute but reversible cardiopulmonary arrest, it has been increasingly applied

to animals with chronic, advanced disease whose prognosis is extremely poor.

Initial survival rates are determined by the nature of underlying disease and the proficiency of resuscitative techniques; early postresuscitation survival is determined by early postresuscitative monitoring and support, and long-term survival is determined by underlying disease.[3]

Survival rates of clinically ill pets are markedly lower than those reported from otherwise healthy experimental animals. A retrospective clinical study of 135 canines and felines who received CPR reported initial resuscitative success in 28 percent of dogs and 42 percent of cats, although only 4 dogs and 1 cat were discharged alive. The discharged animals had cardiac arrests associated with drug or anesthetic reactions.[4] Others report a 9 percent survival rate in dogs[5] and 7 to 22 percent in cats.[6, 7]

When excessive time has elapsed before resuscitation is attempted, CPCR should not be started. When basic life support was started within 1 to 4 minutes of arrest in humans and advanced life support was initiated within 8 to 10 minutes, successful initial resuscitation occurred in 60 percent. In contrast, if basic life support was not started until after 6 minutes and advanced life support was not started until after 12 minutes of arrest, successful resuscitation fell to less than 5 percent.[8] In a model of asphyxia-induced cardiopulmonary arrest, CPCR performed within 3 minutes or less was followed by complete recovery; within 5 minutes, by variable coma and neurologic recovery; and within 7 minutes, by permanent brain damage.[9] This underscores the need for preparedness, training, and coordinated efforts.

Core temperature influences oxygen demand and metabolic rate. In experimental dogs, cerebral ischemia up to 60 minutes at 20°C has resulted in normal neurologic recovery. The metabolic rate and oxygen requirement increases or decreases approximately 7 to 10 percent with every degree Celsius above or below normal.[10] Normothermic animals have been successfully resuscitated up to 12 minutes postarrest,[11] suggesting that efforts may be undertaken in some cases within this time interval.[12] Hypothermia increases the arrest interval from which dogs may be treated.[1, 13]

Prognosis is guarded for animals that do not recover neurologically soon after return of spontaneous circulation. Ideally, ocular reflexes should be present about 5 minutes after restoration of circulation.[2, 11, 14–19] Termination of resuscitation efforts should be considered if mechanical ventilation is necessary for more than 24 hours. Full neurologic recovery should be gained after 2 weeks, although some animals may require several months.

RESUSCITATION DECISION—WHICH ANIMALS TO RESUSCITATE

CPCR should be attempted only in patients in which causes of arrest are believed to be potentially reversible. When doubt exists, resuscitation should be performed.[11, 19] With owners of terminally ill animals, it is prudent to discuss issues regarding "Do Not Resuscitate" (DNR) orders. This will limit fruitless intervention, reduce economic burdens associated with CPR, reduce pet suffering, and minimize owner anxieties.[12]

CLINICAL RECOGNITION

Primary CPA is characterized by loss of consciousness that occurs within 10 to 15 seconds of the event. Pupils become fixed and dilated within 30 to 45 seconds and correspond to electroencephalographic (EEG) quiescence.[11, 14, 20] Capillary refill time (CRT) becomes prolonged, and mucous membrane color may appear muddy gray within 1 to 4 minutes postarrest,[21] although it may remain normal for longer periods in some cases.[2] Breathing ceases, although ventilatory gasps may be observed for up to several minutes. There are no palpable arterial pulses. Secondary CPA usually follows a period of hypoxia, anoxia, acid-base imbalances, or severe hypotension.[15, 22]

Premonitory signs may be noted. They may include azotemia, oliguria, hypotension (systolic pressure < 90 mmHg), reduced pulse pressure, serious brady- or tachyarrhythmias, arterial oxygen saturation measured by pulse oximetry below 85 percent, acidemia, and lactic acidosis. In anesthetized or unconscious pets, decreased respiratory minute volume and reduced arterial blood pressure are common, often appearing before electrocardiographic (ECG) waveforms change. Detection of reduced arterial blood flow may be assessed using Doppler flow devices[16, 19, 21, 22] and other monitoring instruments.[23] Prearrest morbidity indices to predict survival have not yet been established for animals.

RESUSCITATIVE READINESS

PERSONNEL GUIDELINES

Resuscitation requires a team approach. Veterinarians and hospital technicians must be trained in all phases of resuscitation, including upkeep of emergency equipment, instruments, and drugs.[16, 19, 21] A minimum of three individuals trained in resuscitation skills is usually required. Proficiency can be attained through hands-on training facilitated by simulation models such as the CPR DOG (Nasco Company, Fort Atkinson, WI), or by working with cadavers. Duties must be delegated to members of the resuscitation team. The team should review their performance after each CPR effort, to improve proficiency.

EQUIPMENT GUIDELINES

Every practice should have at least one designated and well-equipped "ready area," maintained with a readiness check list (Table 21–1), in which CPCR is performed. A mounted wall chart with emergency drug dosages specified according to body weight is recommended (Table 21–2).[17] Mandatory equipment includes an oxygen delivery system capable of delivering up to 15 liters per minute, an ECG monitor with alligator clip electrodes for rapid attachment, direct current defibrillator, and airway suctioning equipment.[24] A Doppler blood-flow detector, with a pediatric flat flow probe (Parks Medical Electronics, Aloha, Oregon), is highly recommended. A blood pressure cuff placed proximal to the flow probe over the palmar arterial arch allows for arterial blood pressure determination.[25, 26] Other devices are available for blood pressure monitoring (chapter 35). Instruments must be available to perform intubation, emergency tracheotomy, resuscitative thoracotomy, and rapid intravenous fluids (an IV fluid bag should be attached to an administration set and inserted into either a pneumatic [Vital Signs, Inc., Totowa, NJ] or spring-driven [MTM Health Products, Burlington, Ontario, Canada] device to provide fluids under pressure).[17]

BASIC LIFE SUPPORT

Initial efforts are directed toward establishing a patent airway, beginning positive pressure ventilations, and maintaining circulation (Fig. 21–1).

AIRWAY

A patent airway is the first priority in resuscitation. Breathing is assessed over a 5-second period by observing the chest for movement, listening for breath sounds, and feeling for air movement with the rescuer's ear near the mouth. Mouth-to-nose ventilations may be judiciously attempted when no instruments or supplies are available.

Endotracheal Intubation

Ideally, airway securement is accomplished with endotracheal (ET) intubation and followed with positive-pressure ventilation with 100 percent oxygen. For non-obstructed airways, orotracheal intubation using a low-pressure, high-volume cuffed ET tube is the preferred method of basic life support airway management. When possible, the ET tube should be passed without lifting the head higher than the heart as this may decrease brain blood flow in hypotensive patients[17] and increase the chance for aspiration. Passage without a laryngoscope can often be accomplished but requires more manipulation of the epiglottis and may lead to vagotonia and bradycardia.[27] Once in place, the cuff is inflated and the lungs auscultated bilaterally to ensure proper positioning. If there is any concern regarding the possibility of esophageal intubation, the ET tube should be immediately reinserted. If end-tidal CO_2 detectors are attached to the ET (e.g., Easy-CAP, ET CO_2 detector, Nellcor, Hayward, CA), exhaled CO_2 should be easily detectible during ET intubation, but not detectible with esophageal intubation.[28–30]

AIRWAY OBSTRUCTION. The caudal pharynx is a common site of airway obstruction in the comatose pet. Therefore, the head and neck are extended and the tongue drawn forward. Extraneous oral foreign materials are removed if present. If the airway is obstructed by a foreign body and no instruments are available, forceful abdominal and chest compressions are given to simulate a cough in an attempt to clear the airway.[17] Foreign body removal is greatly facilitated by a laryngoscope for visualization and a sponge or tenaculum forceps for extraction. Airway obstructions may require a suction unit capable of generating sufficient negative pressure to aspirate thick mucus and blood clots when the tubing is attached to a dental or Yankauer (tonsil) suction tip.

TRACHEOTOMY. If a patent airway cannot be obtained because of prelaryngeal or laryngeal injury, swelling, spasm, or nondislodgeable foreign bodies, immediate tracheotomy is required. A ventral cervical skin incision is made without aseptic preparation; strap muscles are separated, and the trachea is opened with a transverse incision. The handle end of the scalpel or hemostat is inserted into the lumen followed by an endotracheal tube (a smaller size than used for orotracheal intubation) to allow easy intubation via the tracheotomy.

PERCUTANEOUS TRANSTRACHEAL OXYGEN INSUFFLATION. This technique, using intermittent jet ventilation delivered through a 16-gauge intravenous catheter, has been used successfully to ventilate dogs and cats with airway obstructions.[17] The adapter of a 3-mm ET tube connects to the hub of a catheter needle and then to the Y of the anesthetic tubing and oxygen source. The other end of the Y is occluded with the thumb to control lung insufflation.[31, 32]

TRANSTRACHEAL CATHETER VENTILATION. Another potential technique employs transtracheal catheter ventilation (15 breaths per minute delivered with an oxygen line at 15 L/min flow rates or higher).[33] This method has been effectively used in experimental dogs using

TABLE 21-1
Readiness Check List

CRASH CART

[ ] **Drugs:** all accounted for and expiration dates checked. *Essential:* Epinephrine 1:1000, (1 mg/ml), lidocaine (20 mg/ml), Na bicarbonate (1 mEq/ml), mannitol (25%), dexamethasone sodium phosphate (4 mg/ml), atropine (0.5 mg/ml), furosemide (50 mg/ml). *Recommended:* Dextrose (5%), diazepam (5 mg/ml), dopamine (40 mg/ml), dobutamine (12.5 mg/ml), heparin (1000 U/ml), Ca gluconate (100 mg/ml), oxytocin (10 U/ml), doxapram (20 mg/ml)

[ ] **IV Fluid infusion sets** present; pressure cuff for crystalloid infusion bags working

[ ] **Blood transfusion set** present

[ ] **Endotracheal tubes** in order; cuffs checked for leaks; tie gauze, lidocaine jelly present

[ ] **Laryngoscope** functioning; stylet, mouth gags present

[ ] **Stethoscope** present

[ ] **IV catheters:** Teflon "over the needle" IV venicaths; "butterfly," $\frac{3}{4}''$, 25–18 gauge present

[ ] **Foley and urinary catheters** (all sizes) present

[ ] **Miscellaneous supplies**

- [ ] Syringes (all sizes), surgical tape, bandage material present
- [ ] Needles (25 to 14 gauge), spinal needles (22 and 18 gauge), intraosseous cannulas present
- [ ] Thermometer
- [ ] Orogastric and nasogastric tubes present

MONITORING EQUIPMENT

[ ] ECG machine/monitor working; ECG paper/conduction gel present

[ ] Doppler blood flow detector (changed), flow probe, Aquasonic jelly, blood pressure cuffs present

[ ] Noninvasive blood pressure machine and cuffs checked

[ ] CVP set-up present

[ ] Urinary catheters and collection systems present

OXYGEN-VENTILATION EQUIPMENT

[ ] AMBU bag, masks, rebreathing bag present

[ ] E tanks with at least 500 psi left side, full right side

[ ] Hoses checked for leaks; large and small masks, large and small rebreathing bags present

[ ] Resuscitator bag and tubing (with oxygen line available) present

[ ] Respirator checked and functioning

DC DEFIBRILLATOR

[ ] Defibrillator paddles (internal and external), conduction gel present; defibrillator battery charged

SURGICAL EQUIPMENT AND SUCTION

[ ] **"Wound pack"** and thoracotomy instruments present and sterile, including thumb forceps, needle holder, scalpel blade and handle, medium Finochietto retractors, small and large Balfour retractors, Forester sponge forceps, DeBakey forceps, Mayo scissors (curved), suture material

[ ] Thoracotomy tubes present (cats, small dogs, 14–16 Fr; medium to large dogs, 18–36 Fr)

[ ] Gomco aspirator, Yankauer suction tips, tracheal suction tip present

[ ] Pleurovac present and checked

Inspected by ________________________ Date __________ Time ________ A.M./P.M.

TABLE 21-2
Drugs Commonly Administered for Cardiopulmonary Resuscitation*

Emergency Drugs	Average Dose	*ml/5 lb or/2.3 kg*	*ml/10 lb or/4.5 kg*	*ml/20 lb or/9 kg*	*ml/30 lb or/17 kg*	*ml/40 lb or/18 kg*	*ml/50 lb or/23 kg*	*ml/60 lb or/27 kg*	*ml/80 lb or/36 kg*	*ml/100 lb or/45 kg*
Epinephrine 1:1000 1 mg/ml	0.1 mg/lb (0.2 mg/kg)	0.5	1	2	3	4	5	6	8	10
Lidocaine HCl 20 mg/ml	1 mg/lb** 2.2 mg/kg	0.25	0.5	1	1.5	2	2.5	3	4	5
Na bicarb 1 mEq/ml	0.5 mEq/lb (1.0 mEq/kg)	2.5	5	10	15	20	25	30	40	50
Dexamethasone 4 mg/ml	2 mg/lb (4 mg/kg)	2.5	5	10	15	20	25	30	40	50
Atropine 0.5 mg/ml	0.025 mg/lb (0.05 mg/kg)	0.25	0.5	1	1.5	2	2.5	3	4	5
Calcium gluconate 100 mg/ml	5 mg/lb (10 mg/kg)	0.25	0.5	1	1.5	2	2.5	3	4	5
Countershock										
External	1–10 ws/lb	25	50	100	150	200	250	300	400	500
Internal	0.1–1 ws/lb	2.5	5	10	15	20	20	30	40	50

*Average IV dose: mg/lb or mg/kg (double dose if tracheal route).
**For cats, 0.25 mg/lb (0.5 mg/kg)
ws, watt-seconds.

simple equipment (e.g., transtracheal catheter affixed to a 10-ml syringe barrel connected to a 7.0-mm internal dimension cuffed ET tube) and a low-pressure O_2 delivery source (50 cm H_2O driving pressure).[34]

BREATHING

EMERGENCY VENTILATION WHEN EQUIPMENT IS UNAVAILABLE

Mouth-to-mouth or mouth-to-nose ventilation can be used if resuscitative equipment is not available, although extreme care must be exercised to prevent rescuer injury with agonal pets. This technique has sustained reasonable blood gas values in some cases.[35–37] The animal's mouth must be held closed when the rescuer's mouth is placed over the animal's nose. Exhaled breaths are delivered approximately 12 times per minute (smaller animals may require 12 to 20/min) with an inhalation:exhalation ratio of approximately 1:3 to 1:4. The chest should rise with each ventilation. High airway resistance is commonly encountered, and slower breath delivery may be required (8 to 10 per minute). If air does not enter the lungs, the airway should be re-examined for patency and the tongue repositioned. If resistance is still noted, breaths should be continued using longer "inspiratory times" to achieve lung inflations.[38] Vagotonia may occur when the neck is manipulated and may predispose to parasympathetic-mediated cardiac arrest in severely hypoxemic patients.[39]

Emergency Ventilation Using Equipment and Supplemental Oxygen

Effective ventilation should be optimized with 100 percent oxygen. The lungs are first expanded with two full breaths, using positive end-expiratory pressure (PEEP) created by not allowing the lungs to exhale fully during these initial breaths. Approximately 20 to 25 breaths are given per minute in closed chest CPR, with a 1:2 to 1:3 inhalation:exhalation ratio. Large dogs may require longer inspiratory time and slower ventilation rates. Ventilations should generate a rapid, high (but not sustained) peak airway pressure of 80 to 100 mmHg. Ventilations timed simultaneously with external thoracic compressions provide beneficial hemodynamic effects. If open-chest CPR is initiated, ventilate 40 to 60 breaths per minute, timed simultaneously with direct cardiac compressions (i.e., approximately one ventilation with every second or third compression). Breathing techniques should produce moderate hyperventilation and improve blood gas values. After ventilation is initiated, the chest should be auscultated to assess heart and lung sounds bilaterally. Lung sounds present over one hemithorax only may indicate (1) bronchial intubation, (2) the presence of air, fluid, abdominal contents, or mass in the pleural space, or (3) severe parenchymal lung disease on one side (pneumonia, neoplasia). Repositioning the endotracheal tube, tracheal suctioning, and thoracentesis should be considered.

The partial pressure of arterial carbon dioxide from blood gas analysis defines the ventilatory status and is useful to guide ventilation therapy. The partial pressure of arterial oxygen is a measure of the lung's

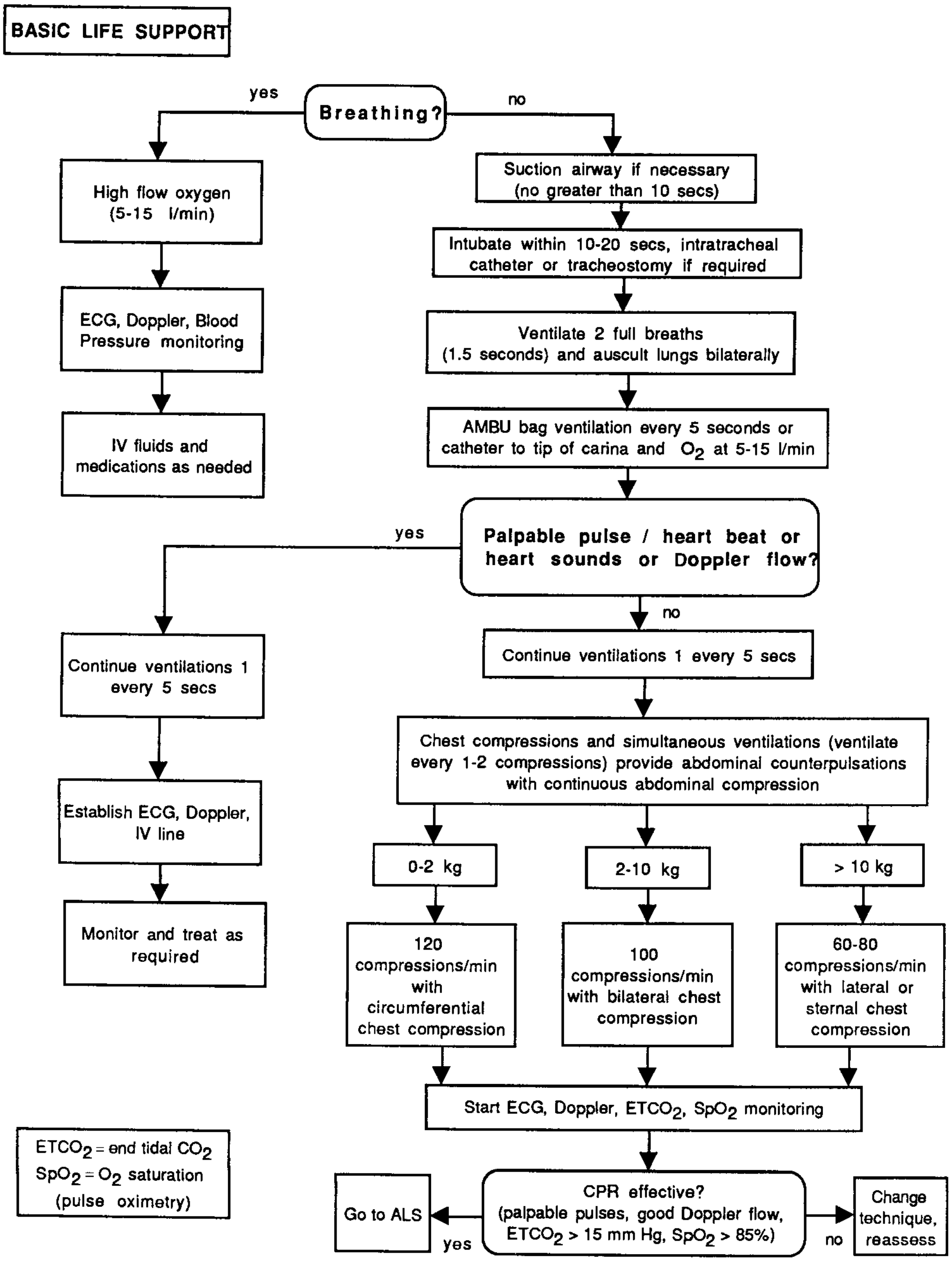


FIGURE 21–1

Clinical algorithm illustrating ideal components of Basic Life Support. ALS, Advanced Life Support (see Fig. 21–2).

capacity to oxygenate the blood (assuming adequate circulation) and is useful to guide positive end-expired airway pressure or percent of inhaled oxygen concentration. If hypoventilation is associated with hypoxemia, the indicated maneuver involves increasing the ventilatory rate or effectiveness, not oxygen therapy.

SUPPLEMENTAL OXYGEN. In the dyspneic but conscious animal, 100 percent oxygen is administered by a "flow-by" technique in which a steady stream of oxygen is directed into the nares. Animals beginning to regain consciousness should have a nasal, nasotracheal, or transtracheal catheter inserted and oxygen continued at a flow rate of 50 to 200 ml/kg/min. Those with endotracheal tubes in place may have a catheter inserted through it with its tip near the carina and oxygen infused at 100 ml/kg/min.[1, 17]

POSITIVE PRESSURE VENTILATION. Animals exhibiting poor ventilatory patterns or low tidal volumes should receive positive-pressure ventilation administered by one of several techniques:

1. *Mouth to endotracheal tube.* This is a temporary initial measure.[36, 37] Ventilation with 100 percent oxygen should be resumed as soon as possible.
2. *Resuscitator (AMBU) bag-valve attached to mask, or mask with oropharyngeal airway to endotracheal tube or to tracheostomy tube.*[36] Use of a reservoir bag or tubing, or a demand valve attached to the AMBU bag, is useful with an oxygen flow rate of 5 to 15 liters per minute.[2, 17]

3. *Anesthetic circuit system to mask; to mask with oropharyngeal airway; to endotracheal tube; or to tracheotomy tube.* Mask ventilation is significantly inferior to the placement and use of an ET tube and should be used only to preoxygenate and provide a few ventilations prior to endotracheal intubation.
4. *Periodic occlusion of ET tube receiving oxygen by tracheal catheter.* Oxygen is delivered at 1 to 5 liters per minute. A thumb or finger is placed over the end of the ET tube; when the lungs are observed to inflate, the thumb or finger is removed to allow exhalation.[36]
5. *Demand valve that runs at 50 psi attached to an AMBU bag.*[1]
6. *Mechanical volume-cycled or timed ventilator.* Pressure-cycled ventilators are not recommended.[1]
7. *High-frequency ventilation (HFV).* This involves administration of short bursts of high-flow oxygen (0.2 to 5 ml/kg) delivered at 90 to 150 breaths per minute.[17] Clinical utility is yet unproved.

TRACHEAL SUCTION. After several effective breaths have been administered, or when resuscitating animals with pulmonary edema or hemorrhage, brief, intermittent tracheal suction may be necessary. Oxygen infusion may be administered through another tracheal catheter during suctioning. Gravity can also be used to empty fluid from large airways by elevating the caudal aspect of the animal in relation to its head.

CIRCULATION

Blood flow must be artificially generated by closed- or open-chest compressions if cardiac arrest pulselessness is detected. Open-chest CPR has been demonstrated to be superior in human trials.[39a]

External Chest Compressions (Closed-Chest CPR)

Vigorous external chest compressions are initiated. Rates vary from approximately 60 compressions per minute for large dogs up to 120 times per minute for cats and small dogs. Brain and heart blood flow is optimal when the force of compression is of relatively long rather than short duration. Compression duration representing approximately 50 percent of the external compression cycle promoted better brain and myocardial blood flow in experimental dogs. Optimal cardiac output was reported at a compression rate of 120/minute.[40, 41]

Circumferential, ventrodorsal, or bilateral chest compressions may be delivered to very small animals (< 2 kg) by squeezing the chest with one hand.[12, 15] Alternatively, digital compression may be applied in a ventrodorsal direction using the fingers placed on the xiphoid-sternal junction, with the animal cradled in the other hand.[41a] In slightly larger animals, the chest is squeezed from both sides, using the thumb placed on one hemithorax and the fingers on the other. Circumferential chest compression has been shown to increase aortic and coronary perfusion pressure in humans[42] but has not been clinically studied in animals.

Lateral thoracic compressions are delivered to animals larger than 5 kg with the pet placed in lateral recumbency. These may be performed by compressing one side of the chest.[43] Alternatively, the nondominant hand may be slid under the chest at the 4th to 6th intercostal space and the dominant hand placed either on the chest wall directly opposite the nondominant hand at or slightly above the costochondral junction (the "heart position"—most effective for animals weighing 5 to 7 kg), or slightly more dorsal at the greatest chest wall diameter (the "thoracic position"—most effective for animals over 10 kg). The former enables the cardiac pump mechanism to generate blood flow; the thoracic position enables the thoracic pump to be as effective as possible (see later). A compression:relaxation ratio of approximately 50:50 is recommended.[24, 44, 45]

The force used to compress the chest should decrease the thoracic wall diameter approximately 25 to 33 percent,[24, 44, 45] although this is difficult to maintain in dogs greater than 20 to 25 kg.[19] If this method is ineffective in generating forward blood flow (e.g., lack of femoral arterial pulses after 1 to 2 minutes of effort), open-chest cardiac massage is immediately performed.

MECHANISMS OF BLOOD FLOW GENERATION WITH CLOSED-CHEST COMPRESSIONS. The heart itself may have less to do with circulation during external chest compressions than previously believed, since cardiac chambers do not fill normally and cardiac valves do not move.[46]

Two basic mechanisms may contribute to forward blood flow generation during chest compression. Blood flow during external chest compression results from the *thoracic pump* mechanism. Increased intrathoracic pressure is immediately transmitted to all intrathoracic vascular structures. Intrathoracic arterial pressure is transmitted to extrathoracic arteries, while retrograde flow from intrathoracic veins is prevented to extrathoracic veins by anatomic closure of venous valves at the thoracic inlet. This causes a gradient across the central nervous system capillary bed, facilitating cerebral perfusion. The thoracic pump mechanism is most prevalent in larger dogs.[44, 47, 48]

Other investigators have demonstrated that cardiac compression does occur in small dogs.[47, 48a] This is referred to as the *cardiac pump* mechanism.

Both the cardiac and thoracic pump mechanisms are thought to be involved with generation of forward flow in animals,[42–44, 49–52] although the latter plays a greater role in dogs over 16 kg.[49]

ADDITIONAL METHOD TO IMPROVE BLOOD FLOW DURING CHEST COMPRESSIONS. Modifications of basic CPR compressions have been studied to increase brain and heart blood flow and improve outcome. Clinical applications of these techniques frequently have been disappointing in humans,[51] although some efficacy has been suggested.[53] Since success following cardiopulmonary arrest is poor, these techniques are described here. However, their value to increase survival in cardiac arrest awaits further investigation.

ABDOMINAL COMPRESSION. Performed only after a cuffed endotracheal tube is inserted (abdominal pressure can cause gastric regurgitation), abdominal compression can be accomplished by wrapping a towel snugly around the abdomen, rear limbs, and pelvic area. This increases systemic vascular resistance, which elevates diastolic and systolic blood pressure.[54, 55] Abdominal compression also limits diaphragm movement during external chest compressions and enhances the thoracic pump mechanism. Canine and feline pneumatic antishock garments (Jobst Inc., Toledo, OH) have been used by some investigators. Excessive abdominal pressure must be avoided, as it will force the liver forward and cause hepatic injury.

INTERPOSED ABDOMINAL COUNTERPULSATIONS. Active abdominal compression is applied to the abdomen (using a 50:50 compression:relaxation ratio) immediately after every chest or heart compression, followed by release of compression pressure immediately prior to the next cycle. Experimentally, this procedure augmented mean arterial blood pressure over conventional CPR,[56, 57] and it has been associated with increased resuscitation rates in humans when compared with chest compressions alone.[53]

SIMULTANEOUS VENTILATIONS AND CHEST COMPRESSIONS. Ventilations given during chest compressions create peak airway pressures as high as 100 mmHg, which, when transmitted throughout the thorax, provides a driving force exceeding that of conventional CPR.[57, 58] In dogs, difficulties have been reported, including hepatic injuries, increased intracranial pressure, pneumothorax, and inadequate gas exchange.[43, 59]

Open-Chest Cardiac Massage

Maintaining oxygenated blood flow to the brain during CPCR is of paramount importance. Standard closed-chest compressions often provide inadequate brain blood flow; an average of only 20 percent of the minimum cardiac output and brain blood flow required to sustain neuronal viability is generated after 5 to 15 minutes of chest compressions.[9, 43, 60] Closed-chest compressions fail to provide adequate perfusion pressures in most cases, even when adjunctive techniques are added.

Because closed-chest CPR is ineffective, even with advanced life support, researchers have investigated methods to improve diastolic perfusion pressure (and thus cerebral flow) and systemic perfusion pressure (for myocardial flow). Open-chest experimental CPR resulted in superior blood flow and better survival and neurologic recovery compared with closed-chest CPR.[61–63]

Open-chest cardiac massage holds a number of advantages. We recommend thoracotomy and open-chest cardiac massage (1) when extraneous factors make external chest compression dangerous or ineffective (Table 21–3) and (2) when closed-chest compression fails to establish spontaneous cardiac activity and arterial pulses after 2 minutes.

EMERGENCY THORACOTOMY. Time is of the essence. Surgical preparation is not performed. A clipper may be passed rapidly in heavily coated or long-haired dogs. The skin is incised on the left lateral chest wall, extending from the rib origin dorsally to near the sternum ventrally. One must avoid incising through intercostal muscles and into the lung. A blunt curved Mayo scissors is used to puncture into the pleural space and the blades are then used to cut through intercostal muscles.[17, 25]

The intercostal space can be enlarged if needed by cutting one or two ribs on the caudal aspect of the incision at their costochondral junction and retracting them with a Balfour abdominal retractor or with a rib spreader, or by a surgical rib pivot procedure.[64]

Other approaches to the chest can be used, including trans-sternal bilateral thoracotomy and parasternotomy. These are more suited for very small patients and animals with thoracic trauma.[17]

The pericardium should be opened immediately after the thoracotomy is completed. The apex of the pericardial sac is cut with Mayo scissors, and the inci-

TABLE 21–3
Factors That May Render Closed-Chest CPR Ineffective

Interference with Generation of High Intrathoracic Pressure
Pneumothorax
Severe pericardial effusion
Severe obesity/very large animal
Diaphragmatic hernia
Flail chest
Tracheal or tracheobronchial disruption
Congenital abnormalities of the chest wall
Conditions Associated with Low Systemic Pressure
Exsanguinating hemorrhage/severe dehydration
Ventricular fibrillation/asystole; electromechanical dissociation
Anaphylactic shock
Gastric dilatation-volvulus syndrome
Anesthetic overdose and prolonged hypoxemia
Drug overdosage

sion is enlarged by moving the scissors dorsally after visualizing and preserving the phrenic nerve. Pericardiotomy facilitates detection of ventricular fibrillation and increases effectiveness of CPCR.

When a stable, spontaneous cardiac rhythm is obtained, the chest is lavaged and systemic antibiotics administered. The incidence of infection following resuscitative thoracotomy without prepping in our experience is less than 10 percent.

DIRECT CARDIAC MASSAGE TECHNIQUE. One or both hands are used depending on patient size. Care should be taken to avoid "kinking" the great cardiac vessels, which may occur if the apex is manually tipped laterally upward. Very small hearts may allow the ventricles to be compressed between the thumb and two fingers. For medium-sized hearts, the ventricles are compressed between the rescuer's palm and the palmar surface of the fingers. Large hearts may be held against the opposite chest wall and compressed by holding the ventricles in the palm of one hand.

The rate of direct massage should be between 80 and 120 per minute. The adequacy of diastolic filling should be visually determined. The heart should fill as soon as it is released. If not, vascular occlusion or "kinking" should be evaluated or fluid administration considered. The heart should also be observed for myocardial color, tone, and the presence of fibrillation. Ventilation should be timed to occur with every second or third compression if possible.

DESCENDING AORTA COMPRESSION AND CROSS-CLAMPING. To improve cerebral perfusion and coronary circulation, the descending aorta should be occluded. This may be accomplished by digitally compressing it against the vertebral column using simple pressure. Alternatively, cross-clamping may be performed just caudal to the heart base. In the trauma patient, aortic cross-clamping will temporarily retard severe arterial hemorrhage in the chest, abdomen, retroperitoneum, and pelvis. Occlusion may be facilitated by a flexible soft material used for a "tourniquet," such as 3.5 to 5 French feeding tube, 0.25- to 0.50-inch umbilical tape, or Penrose drain. Use is limited to less than 10 minutes to avoid pelvic limb paraplegia. A curved hemostat is used to dissect around the caudal thoracic aorta. The tip of the material is grasped and pulled around the aorta to form a loop. The same hemostat is then slid down on the loop to tighten it around the aorta. After the heart begins contracting spontaneously, the tourniquet is slowly withdrawn (rapid removal may result in hypotension). Occlusion time should be kept to less than 10 minutes.

ADVANCED LIFE SUPPORT

Following the basic cardiac life support measures discussed earlier, advanced life support is promptly initiated to restore spontaneous and effective circulation (Fig. 21–2). It has three components: **D**—*drug* administration required to increase brain and myocardial blood flow, optimize blood pressure, and treat cardiac arrhythmias or acidosis, and *defibrillation* for ventricular fibrillation; **E**—*electrocardiographic* and other systemic monitoring; and **F**—continued support as required to maintain adequate *blood flow.*

RECOMMENDED ROUTES OF DRUG ADMINISTRATION

Several routes of drug adminstration are available. Intravenous or intraosseous routes are preferred and necessary when continuous rate infusions are given, or for crystalloid, colloid, or blood administration.[25, 65]

Intravenous

Rapid intravenous access should be used on any identifiable vessel that can be cannulated. Circulation times may vary according to vascular site and type of CPR. In an experimental model of canine cardiopulmonary arrest, drug circulation times of 62 ± 19.6 seconds were recorded after central venous injections; 86.6 ± 23.5 seconds after femoral venous injections; and 93.6 ± 17.9 seconds after cephalic venous injections.[66] In contrast, circulation times with open-chest cardiac massage were considerably shorter (21.3 ± 5.7 seconds after central venous injections; 33.7 ± 5.1 seconds after femoral vein injections; and 31.4 ± 6.0 seconds after cephalic injections). Drug concentrations were best circulated by the central venous compared with other routes. In open chest resuscitation, drug concentrations were greatest when administered by central venous injection compared with the cardiac route.[67]

Commonly selected peripheral venous sites include the external jugular, femoral, and saphenous veins; the maxillary vein also may be used effectively.[25, 68]

Transtracheal or Endotracheal

These routes have been recommended for initial delivery of relatively small volumes of emergency drugs when central intravenous or intraosseous catheter placement is not feasible.[2, 16, 21, 24, 69] Drugs are generally given at two to three times the intravenous dose, diluted in 5 to 10 ml of saline, and injected transtracheally or, more commonly, into a long catheter placed through the ET tube, with its tip inserted to the level of the carina.[1, 70, 71] The animal should then be ventilated to help distribute the drug.

Uptake is rapid via this route as long as pulmonary edema or severe hemorrhage is not present. Lipophilic

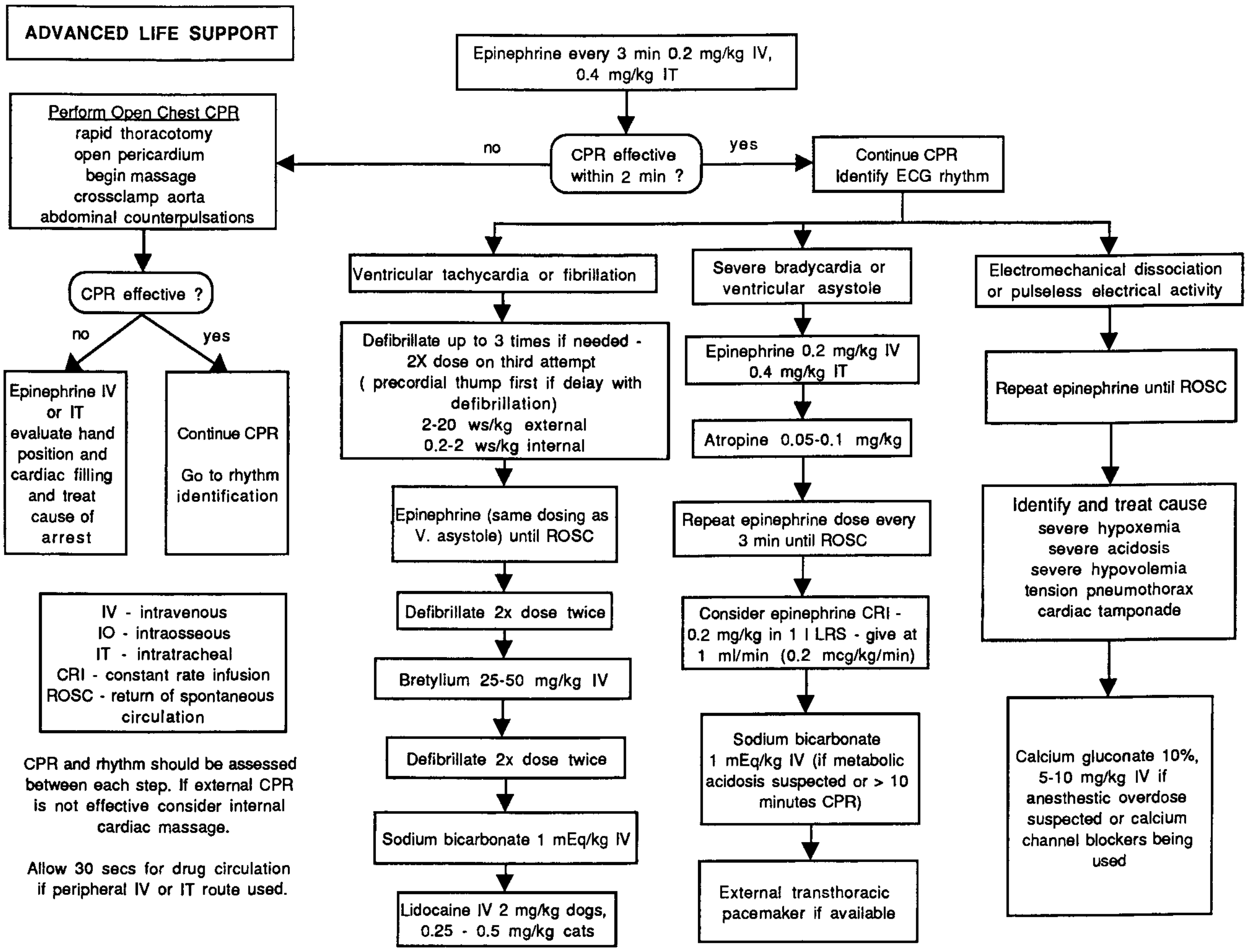


FIGURE 21–2

Clinical algorithm illustrating ideal components of Advanced Life Support. CRI, constant rate infusion; LRS, lactated Ringer's solution; V, ventricular; epinephrine = 1:1000 concentration.

drugs are rapidly absorbed, and relatively sustained blood concentrations can be achieved. Epinephrine is the drug most commonly administered in this fashion.[2, 12, 21, 24, 70–72] Lidocaine, atropine, diazepam, bretylium, propranolol, isoproterenol, and naloxone have been similarly administered.[72] Calcium, sodium bicarbonate, and norepinephrine may injure airway mucosa and alveoli and should not be given via the endotracheal route.[24] In dogs, peripheral bronchial administration (i.e., via a 16-gauge catheter introduced through the ET tube and peripherally wedged in a bronchus) has demonstrated a clear pharmacologic advantage over just endotracheal administration.[73]

Intraosseous

This route been found useful in dogs;[73, 74] in kittens, puppies, birds, pocket pets, and small exotics, it is useful as a first-line administration route. The abundant endosteal-medullary blood supply facilitates rapid uptake of fluids and drugs. An 18- to 20-gauge hypodermic or spinal needle (preferred) can be used effectively, as well as commercially available intraosseous needles.

Intracardiac

For external chest compressions, the intracardiac route is not recommended because of the need to interrupt this activity and the possibility of lacerating a coronary vessel and creating pneumothorax.[1, 24] Despite these concerns, this route has been recommended when no other is available.[75] During open-chest resuscitation with the heart visualized, this may be a useful central route for drug administration.[21] Following a left ventricular injection, a finger should occlude the ascending aorta during the next few cardiac compressions to promote drug injection into the coronary circulation.

Intralingual

Because uptake is unpredictable, intralingual administration has been recommended as a last resort by

some workers.[65] Others have found it occasionally useful.[12] Drugs limited to moderately small volumes (1 to 15 ml) are injected just under the dorsal mucosal tongue surface.

EFFECTIVE INTERVENTIONS FOR CARDIOPULMONARY ARREST

Prompt endotracheal intubation, basic life support, and epinephrine administration represent the principal steps to successful CPR. The key to optimizing cerebral recovery and overall survival when ventricular fibrillation or pulseless ventricular tachycardia is present is rapid defibrillation to restore spontaneous circulation. Endotracheal intubation facilitates ventilation and oxygenation of the poorly perfused myocardium. Myocardial perfusion is necessary for effective defibrillation. Epinephrine causes vasoconstriction, supporting coronary perfusion pressure. Additional agents such as antiarrhythmics, synthetic catecholamines other than epinephrine, and glucocorticosteroids play a role only occasionally.

DRUGS FOR CARDIOPULMONARY RESUSCITATION

EPINEPHRINE AND OTHER ALPHA-ADRENERGIC AGENTS

Considering all pharmacologic agents used for CPR, none have proved as useful as epinephrine. Within minutes of cardiopulmonary arrest, extensive vasodilation results from metabolic byproducts associated with tissue anoxia.[76] This causes ineffectual tissue blood flow, particularly to the brain and heart, despite basic life support techniques. Through its α-adrenergic receptor stimulation, epinephrine stimulates vasoconstriction, especially of peripheral vasculature. These pressor effects increase aortic diastolic and coronary perfusion pressures and are central to its efficacy (i.e., raising aortic diastolic pressure improves coronary blood flow). Epinephrine administered during CPR at relatively high doses (0.2 mg/kg) has been reported to cause increased effectiveness in human adults, children, swine, and dogs over previously suggested "standard doses" (0.01 mg/kg),[77-80] although recently, some investigators have called this into question.[81]

Other pure α-adrenergic agonists have the theoretic advantage of stimulating less myocardial oxygen consumption than agents like epinephrine, which has both α- and β-adrenergic actions.[82] However, there has been no convincing evidence to date that pure α-adrenergic agents are superior to epinephrine in CPA to restore spontaneous circulation and promote neurologic recovery.[83]

The optimal dosing regimen is not clear, although the American Heart Association standards and guidelines recommend epinephrine administration every 5 minutes during CPR. Thus, it is recommended that epinephrine be immediately administered by intravenous or intraosseous bolus (0.2 mg/kg), or by intratracheal administration (0.4 to 0.8 mg/kg followed by 5 to 10 ml of saline) as a second route of choice. Because of the short half-life (3 to 4 minutes), constant rate infusion (0.1 to 2.0 μg/kg/min CRI) or IV boluses repeated every 3 to 5 minutes are recommended.[72] A quick rule of thumb method to calculate a constant rate epinephrine infusion of 2 μg/kg/min involves multiplying 0.2 mg/kg times body weight, placing this volume of epinephrine into 1 liter of fluids, and administering it at 1 ml per minute (if a volume of 500 ml or 250 ml is desired, multiply body weight by 0.2 mg/kg body weight and infuse at 0.5 ml/min or 0.25 ml/min, respectively).

LIDOCAINE

In general, the second agent to be considered in canine CPA is lidocaine hydrochloride. It is the ventricular antiarrhythmic drug of choice for unstable ventricular arrhythmias (chapters 17, 18). Lidocaine raises the threshold for ventricular fibrillation[84] and results in only minimal hemodynamic impairment in dogs, unless severe myocardial failure or greatly reduced clearance is present.[85] Lidocaine's effects may be compromised in the presence of hypokalemia.[86, 87]

For dogs, an initial intravenous loading bolus (2.2 mg/kg), followed by constant intravenous infusion (25 to 75 μg/kg/min) with small supplemental IV boluses as needed, will rapidly attain and maintain therapeutic plasma concentrations.[86, 88]

Cats must be given greatly reduced dosages of lidocaine. Experimentally, toxic manifestations were reported with 10 mg/kg[89] given by rapid IV injection, and at a mean dosage of 11.7 mg/kg.[90] However, clinically affected cats during CPA and shock tolerate far less lidocaine since hepatic metabolism and blood flow may be greatly reduced. Conversion of ventricular tachycardia in cats has been successful by administering lidocaine by slow IV infusion (0.25 to 1.0 mg/kg over 5 minutes[91]) or using up to three 1-mg IV boluses.[92]

OTHER ANTIARRHYTHMICS

Bretylium tosylate also raises the fibrillation threshold, but it may be more useful in preventing ventricu-

lar fibrillation in dogs at risk, such as dogs who were just defibrillated, or with arrhythmias likely to lead to ventricular fibrillation.[93] However, its clinical effects have not been well characterized in veterinary practice.

SODIUM BICARBONATE

A controversial area of cardiac arrest therapy involves therapy for acid-base abnormalities. Traditional recommendations for its early administration were based on the premise that bicarbonate helped counter metabolic acidosis generated by anaerobic metabolism during hypoxia. Empiric administration of bicarbonate in an experimental canine model of CPR showed improved outcome.[93a]

However, current guidelines argue against routine bicarbonate administration and stress the importance of appropriate ventilation, oxygenation, and circulatory support to control acidosis. Mixed venous acidemia occurs with cardiac arrest and respiratory acidosis.[94] Sodium bicarbonate administration can increase blood carbon dioxide tension (PCO_2) as per the bicarbonate dissociation equation ($H^+ + HCO^+_3 \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$), which is driven to the right toward CO_2 formation. This worsens venous respiratory acidemia. In addition, tissue CO_2 production continues and accumulates in the venous system. For CO_2 to be eliminated, venous blood must be returned to the heart and pumped to the lungs, a process impaired during arrest. Carbon dioxide diffuses readily across tissue membranes. Central nervous system and intracellular acidosis worsen. Myocardial "CO_2 narcosis" may reduce cardiac function and the ability to resuscitate the heart and may predispose to electromechanical dissociation.[95–97]

Routine bicarbonate use is not currently advocated except when venous blood gas values or the patient's history indicates severe metabolic acidosis after prolonged CPR efforts. Alternatively, bicarbonate can be administered (0.5 to 1.0 mEq/kg IV) after at least 10 to 15 minutes during the low-flow stage of CPR, or if a long interval transpired prior to CPR initiation. Care must be taken to provide adequate and effective ventilation.

OTHER AGENTS

Anticholinergics are administered for severe sinus bradycardia and AV block caused by high vagal tone when reduction of the inciting vagotonia is ineffective (e.g., atropine, 0.02 to 0.04 mg/kg intramuscularly or subcutaneously). Intravenous administration may exacerbate sinus bradycardia and cause temporary atrioventricular block through a centrally mediated increase in vagal tone (chapter 38).[98, 99] *Calcium* administration during CPR is of doubtful value and may be harmful. Postresuscitation brain injury results from a cascade of detrimental events initiated by brain hypoxia and ischemia. Loss of intracellular calcium ion homeostasis is a key factor responsible for cell disruption and death and is associated with increased intracellular calcium.[100–102] For electromechanical dissociation, epinephrine and perhaps steroids rather than calcium should be administered. Calcium administration is contraindicated except for severe hypokalemia, hypocalcemia, or calcium channel blockade toxicity. *Calcium entry blockers* have been shown experimentally to prevent postresuscitation brain hypoperfusion[103] and improve resuscitation.[104] However, they are not advocated at this time because of potential vasodilating effects and depression of cardiac conduction.

Dexamethasone sodium phosphate (2.0 to 4.0 mg/kg IV) has been advocated for treating electromechanical dissociation.[16, 105] *Corticosteroids* may be beneficial in maintaining cell membrane integrity and in converting electromechanical dissociation. *Dopamine* may be administered by constant rate infusion (1 to 2 μg/kg/min) to increase renal blood flow, or for its pressor (α-adrenergic agonist) effects (5 to 10 μg/kg/min) to treat hypotension unresponsive to other therapies.[106] Other pressors may be alternatively employed. *Crystalloids, colloids,* or *blood* may be required for rapid volume fluid replacements if severe hypovolemia (e.g., hemorrhage, severe vomiting and diarrhea, pleuritis, peritonitis, and noncardiogenic shock) contributed to or was associated with the arrest. *Isoproterenol* causes increased myocardial oxygen demand through increased contractility and peripheral vasodilation (β-adrenergic effect) and is not advocated in CPR.[107] *Mannitol* (0.5 g/kg, slow IV infusion) may be warranted for cerebral edema. *Furosemide* and other cardioactive agents are required for managing heart failure.

DEFIBRILLATION

Rapid conversion to a stable, effective rhythm is critical for successful resuscitation when ventricular fibrillation, pulseless idioventricular rhythm, or pulseless ventricular flutter/fibrillation is detected or suspected in the absence of an ECG monitor.[108] Early direct current defibrillation causes myocardial depolarization, ensuing asystole, and (it is hoped) return of ordered sinoatrial or other pacemaker-initiated depolarization-repolarization sequences. Factors that influence successful defibrillation include (1) patient transthoracic resistance and resultant current flow, (2) energy level, (3) paddle size, (4) body weight, (5) metabolic abnormalities, and (6) duration of ventricular fibrillation prior to shock. There is an inverse corre-

lation between duration of ventricular fibrillation and successful defibrillation.[109]

Transthoracic resistance may increase more as a function of chest width than body weight and can be reduced with large paddles and firm contact pressure. Transthoracic resistance and current flow are minimal with a second shock delivered at the same energy level.[110] Thus, titration of shocks to higher energy levels may improve chances for successful defibrillation. Excessive energy can cause myocardial injury.[111] Approximate power settings (watt-sec) for small patients are external: 50 to 100; internal: 10 to 25. For large patients, external: 100 to 360; internal: 25 to 100.

If there is no conversion after two or three concurrent titrated shocks, the patient should receive epinephrine (0.2 mg/kg IV or 0.4 mg/kg intratracheally), followed by another maximum countershock relative to patient size. If pulseless ventricular tachycardia continues, a lidocaine bolus (2.2 mg/kg IV for dogs; 1 to 2 mg IV for cats) is administered, followed by an additional shock. Failure to convert to a stable rhythm at this time is a poor prognostic indicator. Therapy should then be refocused to correct underlying acid-base and metabolic derangements by improving oxygenation and reducing metabolic acidosis through effective ventilation, and by providing effective circulation (e.g., consider open-chest CPR if closed-chest CPR is being performed). Epinephrine can be readministered. Sodium bicarbonate may be empirically given under conditions of known prolonged resuscitation time or failure to convert to a stable rhythm. If the patient transiently converts to a stable rhythm but the arrhythmia returns, the same countershock is reapplied.

If a defibrillator is not available when ventricular fibrillation or pulseless ventricular tachycardia is encountered, a precordial thump can be delivered.[112] The odds of effecting spontaneous conversion are low, but so is the associated risk. Lastly, chemical defibrillation has been described, using a mixture of acetylcholine (6 mg/kg)[113] or potassium chloride (1 mEq/kg), followed by 10 percent calcium chloride (0.2 ml/kg).[7]

CLINICAL MONITORING AND EVALUATION

A global approach to patient monitoring incorporates medical history and physical examination supplemented with information gained through clinical, physiologic, clinical pathology, and radiographic testing. Monitoring should (1) assess physiologic derangements caused by organ hypoperfusion and hypoxia, (2) detect end-organ dysfunction, and (3) evaluate therapy.[114] It is important to assess as many parameters of cardiovascular and organ performance, oxygen transport, and tissue perfusion as possible.

PERIPHERAL PERFUSION

Mucous membrane color and refill time, urine output, and toe web temperature provide some assessment of peripheral and visceral organ perfusion that is largely regulated by vasomotor tone. Vasoconstriction (or reduced blood volume) decreases peripheral perfusion and may cause pale mucous membrane color, prolonged capillary refill time, oliguria/anuria, and hypothermia. Vasodilation improves peripheral perfusion but, if extensive, may result in hypotension.

MUCOUS MEMBRANE COLOR

Skin or mucous membrane color is used as a crude assessment of tissue oxygenation, but it is really a rough estimate of hemoglobin oxygenation. Before cyanosis associated with hypoxemia can be detected, circulation of at least 5 gm/dl of deoxygenated hemoglobin must be present. Pale gray mucous membranes may result from cyanosis combined with peripheral vasoconstriction. Pink or reddish mucous membrane may be observed during initial stages of septic shock. Injected, dark red mucous membranes may result from cyanosis combined with hypoxemia and reduced blood flow.[114]

HEART SOUNDS

Heart sounds become softer and, ultimately, undetectable by auscultation when cardiac blood flow becomes severely reduced or ceases. This may result from shock, myocardial failure, ventricular underfilling (e.g., cardiac tamponade), or low circulatory states. Muffled heart and lung sounds may also result from pneumothorax, severe pericardial or pleural effusions, or thoracic masses.

HEART RATE

Tachycardia results from increased sympathetic nervous system activation from any cause. Since cardiac output is the result of stroke volume multiplied by heart rate, tachycardia may develop during conditions associated with hypovolemia, heart failure, systemic and metabolic disease, and impending cardiac arrest. Bradycardia is often a preterminal or terminal event common to many animals with cardiopulmonary arrest. It can also develop from vagotonia.

ELECTROCARDIOGRAPHIC MONITORING

Heart rate and rhythm are extremely labile in critically ill animals, especially when cardiac arrest has occurred or is impending. Continuous ECG monitoring may disclose important clues indicating (1) cardiovascular deterioration (e.g., progressive bradycardia, atrioventricular dissociation, or ST-T wave changes), (2) electrolyte disorders (e.g., hyperkalemia [tall, peaked T waves; prolonged PR interval; flattened or absent P waves; QRS prolongation]; hypokalemia [flattened T waves; lengthened QT intervals; ST segment changes]), (3) ST and T wave changes associated with hypoxia, infarction, or electrolyte changes, or (4) indication of clinical improvement (e.g., reversal of abovementioned ECG changes) or antiarrhythmic therapy efficacy.[115, 116] Although it is important to identify and monitor the cardiac rhythm, it must be remembered that only electrical activity is being monitored, which does not provide information concerning myocardial function or effective circulation. Arrhythmias reported during cardiopulmonary arrest included ventricular asystole (24 percent in dogs; 18 percent in cats); electromechanical dissociation (21 percent vs. 34 percent); ventricular fibrillation (21 percent vs. 14 percent); sinus bradycardia (18 percent vs. 16 percent); and ventricular tachycardia (4 percent vs. 4 percent).[115]

ARTERIAL PULSES

Arterial pulses are governed by left ventricular stroke volume, arterial compliance, and capacity (chapter 35). Lack of palpable arterial pulse is an indicator of cardiopulmonary arrest or hypotension. Studies in anesthetized animals report variable systolic pressures associated with loss of palpable femoral arterial pulses (40 to 80 mmHg) and palpable heart beat (30 to 55 mmHg).[2, 25, 117] Variability depends on clinician experience, animal size and conformation, and vascular tone. Chest compressions should be started immediately when pulselessness is recognized. Exaggerated arterial pulses may occur with anemia, fever, sympathetic hyperactivity, or severe bradycardia; weakened arterial pulses may occur with severe tachycardia and hypovolemia (i.e., weak, thready pulses associated with reduced stroke volume and vasoconstriction).

ARTERIAL BLOOD PRESSURE MONITORING

Trends in arterial blood pressure can be monitored invasively or noninvasively (chapter 35), which provides essential information to guide therapy and assess hemodynamic status. As a general guide, it is desirable to maintain systolic arterial pressure over 100 mmHg and mean pressure over 70 mmHg. Therapy is generally warranted with a systolic pressure of less than 80 mmHg and a mean pressure of less than 60 mmHg.

QUALITATIVE DOPPLER BLOOD FLOW MONITORING

A pediatric blood flow probe (Model 811B, Parks Medical Electronics, Aloha, OR) can be useful to provide a general, qualitative indicator of arterial blood flow.[12, 23, 25, 26, 37, 117] It may also help evaluate the relative effectiveness of chest or cardiac compression when attempting to generate forward blood flow.

OXYGEN TRANSPORT AND TISSUE PERFUSION

Microcirculatory maldistribution results in tissue hypoxia and anoxia (chapter 14). Circulating blood volume is the most important factor affecting tissue perfusion and oxygen delivery. Systemic tissue oxygen transport is defined as the product of cardiac output and arterial oxygen content ($TO_2 = CO \times CaO_2$). The main determinants of tissue oxygen transport are arterial oxygen content (CaO_2) and cardiac output (CO). Major determinants of CaO_2 are hemoglobin concentration (Hb), which is indirectly assessed by packed cell volume (PCV), and degree of Hb saturation, which can be evaluated by pulsed oximetry. Thus, $CaO_2 = Hb \times 1.34 \times SaO_2$. The major determinants of cardiac output are heart rate and stroke volume ($CO = HR \times SV$).[114]

HEMOGLOBIN SATURATION MONITORING BY PULSE OXIMETRY

Estimation (percent) of hemoglobin oxygen saturation (SpO_2) may be made by pulse oximetry instruments using infrared light sensors applied to mucous membranes or skin.[118, 119] The pulse oximeter allows continuous monitoring of hemoglobin saturation, although most instruments are designed for human use and often have trouble recording SpO_2 transcutaneously. Normal SpO_2 recordings depend somewhat on probe placement site, with the tongue and lip considered the best sites.[119] Normal SpO_2 values exceed 96 percent. Lower values may indicate relative oxygen desaturation and hypoxemia, which could increase the risk for cardiopulmonary arrest.[65] The accuracy of pulse oximetry readings in dogs may be diminished at low saturation.[120]

BLOOD GAS ANALYSIS

Arterial blood oxygen may be expressed as (1) the partial pressure of oxygen (PaO_2), (2) the percent hemoglobin saturation (SpO_2), and (3) the arterial oxygen content (CaO_2). These measurements are interrelated but not synonymous. Arterial carbon dioxide is expressed as the partial pressure of CO_2 ($PaCO_2$). Ventilatory status is assessed by $PaCO_2$. The lung's ability or efficiency to oxygenate the blood is indicated by PaO_2.[7, 114] Blood pH identifies the severity of acid-base derangement.

PARTIAL PRESSURE OF OXYGEN

Arterial PO_2 (PaO_2) is a measure of pulmonary oxygenating efficiency. Hypoxemia is considered present when PaO_2 is less than 60 mm Hg. An animal may have normal PaO_2, yet still have reduced blood oxygen content if anemia or methemoglobinemia is present. Hypoventilation is correlated with hypoxemia when the animal is breathing room (but not oxygen-enriched) air.[7]

PARTIAL PRESSURE OF CARBON DIOXIDE

Arterial PCO_2 ($PaCO_2$) indicates a measure of ventilatory status (normal, 35 to 45 mmHg). It should be assessed in concert with PaO_2, since both parameters tend to change in opposite directions relative to each other. Hyperventilation is indicated by a $PaCO_2$ of less than 35 mmHg, and less than 20 mmHg is associated with severe respiratory alkalosis; hypoventilation is indicated by a $PaCO_2$ greater than 45 mmHg ($>$ 60 mmHg indicates severe respiratory acidosis, hypoventilation, and possibly hypoxemia if breathing room air).[7] End-tidal carbon dioxide monitoring may be accomplished with a capnograph through sensors affixed to the end of an ET tube. End-tidal CO_2 values greater than 15 mmHg indicate that CO_2 is reaching the alveoli and pulmonary gas exchange is occurring, implying some effectiveness of CPCR.[38, 52] Values lower than this indicate poor blood flow and/or inadequate respiratory exchange. End-tidal CO_2 correlates only variably with $PaCO_2$.[30, 121]

ARTERIAL AND VENOUS CATHETERIZATION

Central venous catheterization (intrathoracic anterior vena cava or right atrium via the jugular vein) allows central venous pressure (CVP) monitoring. The CVP measurement results from interrelationships among right ventricular function, venous return, and vascular volume and is useful to guide the rate (but not volume) of fluid administration. It should be interpreted in relation to other cardiovascular parameters. A large, acute increase in CVP ($>$ 5 to 7 cm H_2O), or a reading of greater than 10 cm H_2O during fluid administration, may indicate an excessively rapid fluid administration rate.

Pulmonary artery catheterization allows measurements of pulmonary wedge pressure, an index of left ventricular filling (greater than 15 to 20 mmHg may herald pulmonary edema), pulmonary artery pressure, and cardiac output. It facilitates mixed venous blood sampling to assess and derive oxygen transport variables.

Peripheral arterial catheterization facilitates arterial blood sampling and provides access for continuous direct blood pressure monitoring.

CLINICAL PATHOLOGY AND OTHER ASSESSMENTS

Multiorgan function or tissue injury may be evaluated by appropriate clinical pathology, including biochemical profiles, hemograms, and urinalysis. Blood coagulability tests and platelet counts should be assessed to detect disturbances in blood clotting. Radiography is useful to detect and uncover underlying disorders or untoward effects resulting from CPR, such as pneumothorax, pulmonary contusion or edema, and rib fractures.

POSTRESUSCITATION BRAIN-ORIENTED THERAPY

Clinical deterioration of neurologic status resulting from cardiac arrest is triggered by initial ischemia and exacerbated by subsequent reperfusion. This may cause irreversible brain damage and worsen survival. Pathophysiology may be related to (1) cerebral reperfusion failure;[122] (2) cerebral reoxygenation injury from cell-necrotizing cascades perhaps related to calcium shifts and free radical reactions;[123, 124] and (3) blood toxemia associated with microcirculatory stasis and tissue factors.[125] Accordingly, emphasis during CPR is increasingly placed on preserving the integrity of neuronal brain function. The challenge for cerebral resuscitation is to direct interventions to overcome these complex mechanisms and improve cerebral outcome. Certain postresuscitation life support protocols being evaluated in human medicine[126] potentially may prove useful for dogs and cats.

REFERENCES

1. Safar P, Bircher NG. Cardiopulmonary Cerebral Resuscitation. 3rd ed. Philadelphia, WB Saunders, 1988
2. Wingfield WE, Henick RA. Cardiopulmonary arrest and resuscitation. *In* Ettinger SJ (ed): Textbook of Veterinary Internal Medicine. 3rd ed. Philadelphia, WB Saunders, 1989, p 171
3. Haskins S. Cardiopulmonary resuscitation. *In* Emergency Medicine and Critical Care in Practice. Trenton, NJ, Vet Learning Systems Company, 1992, p 71
4. Kass PH, Haskins SC. Survival following cardiopulmonary resuscitation in dogs and cats. Vet Emerg Clin Care 2:57, 1992
5. Gilroy BA. Survival after cardiopulmonary resuscitation in canine patients. Proc Vet Emerg Crit Care Soc 196, 1986
6. Henick RA. Cardiopulmonary arrest and resuscitation in cats. Proc Vet Emerg Crit Care Soc 66, 1987
7. Gilroy BA. Survival after cardiopulmonary resuscitation in feline patients. Proc Vet Emerg Crit Care Soc 201, 1986
8. Carveth SW. Eight-year experience with a stadium-based mobile coronary-care unit. Heart Lung 3:770, 1974
9. Safar P. Long-term animal outcome models for cardiopulmonary cerebral resuscitation research. Crit Care Med 13:936, 1985
10. Tisherman SA, Safar P, Radovsky A, et al. Therapeutic deep hypothermic circulatory arrest in dogs: A resuscitation modality for hemorrhagic shock with "irreparable" injury. J Trauma 30:836, 1990
11. Gilroy BA, Rockoff MA, Dunlop BJ, et al. Cardiopulmonary resuscitation in the nonhuman primate. J Am Vet Med Assoc 177:867, 1980
12. Robello CD, Crowe DT. Cardiopulmonary resuscitation: Current recommendations. Vet Clin North Am 19:1127, 1989
13. Tisherman S, Chabal C, Safar P, et al. Resuscitation of dogs from cold-water submersion. Ann Emerg Med 14:389, 1985
14. Gilroy BA, Dunlop BJ, Shapiro HM. Outcome from cardiopulmonary resuscitation in cats: Laboratory and clinical experience. J Am Anim Hosp Assoc 23:133, 1987
15. Wingfield WE, Van Pelt DR. Respiratory and cardiopulmonary arrest in dogs and cats: 265 cases (1986–1991). J Am Vet Med Assoc 200:1993, 1992
16. Crowe DT. Cardiopulmonary resuscitation in the dog: A review and proposed new guidelines (part 2). Semin Vet Med Surg (Small Anim) 3:328, 1988
17. Crowe DT. Triage and trauma management. *In* Murtaugh RJ, Kaplan PM (eds): Veterinary Emergency and Critical Care. St. Louis, Mosby–Year Book, 1992, p 77
18. Safar P. Cardiopulmonary cerebral resuscitation: Basic and advanced life support. *In* Schwartz GR, Safar P, Stone JH, et al (eds): Principles and Practice of Emergency Medicine. 2nd ed. Vol 1. Philadelphia, WB Saunders, 1978, p 195
19. Crowe DT. Cardiopulmonary resuscitation in the dog: A review and proposed new guidelines (part 1). Semin Vet Med Surg (Small Anim) 3:321, 1988
20. Hossman KA. Resuscitation potentials after prolonged cerebral ischemia in cats. Crit Care Med 16:964, 1988
21. Crowe DT: Cardiopulmonary resuscitation and advanced life support. *In* Zaslow IM (ed): Veterinary Trauma and Critical Care. Philadelphia, Lea & Febiger, 1984, p 507
22. Crile GW, Dolley DH. An experimental research into the resuscitation of dogs killed by anesthetics and asphyxia. J Exp Med 8:713, 1906
23. Paradis NA, Martin GB, Goetting MG, et al. Aortic pressure during human cardiac arrest: Identification of pseudo-electromechanical dissociation. Chest 101:123, 1992
24. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). J Am Med Assoc 268:2171, 1992
25. Crowe DT. Performing life-saving cardiovascular surgery. Vet Med 84:77, 1989
26. Grandy J, Dunlop C, Hodgson D. Evaluation of the Doppler ultrasonic method of measuring systolic pressure in cats. Am J Vet Res 53:1166, 1992
27. DeBehnke DJ. Effects of vagal tone on resuscitation from experimental electromechanical dissociation. Ann Emerg Med 12:1789, 1993
28. Sayah AJ, Peacock WF, Overton DT. End-tidal CO_2 to detect esophageal intubation during cardiac arrest. Ann Emerg Med 19:857, 1990
29. Coates NE. End-tidal carbon dioxide predicts the emergency department survival of traumatically injured, intubated patients; Abstract. Crit Care Med 22:A137, 1994
30. Falk JL, Rackow EC, Weil MH. End-tidal carbon dioxide concentration during cardiopulmonary resuscitation. N Engl J Med 318:607, 1988
31. Spoerel WE, Narayanan PS, Sinph NP. Transtracheal ventilation. Br J Anaesth 43:932, 1971
32. Wilson DV, Orsher RJ. Transtracheal ventilation for resuscitation after complete airway obstruction in a cat. J Am Anim Hosp Assoc 27:331, 1991
33. Kumar M, Murry MJ. Prophylactic percutaneous transtracheal catheter ventilation in the management of the difficult airway; Abstract. Crit Care Med 22:A130, 1994
34. Reich DL, Mingus M. Transtracheal oxygenation using simple equipment and a low-pressure oxygen source. Crit Care Med 18:664, 1990
35. Elam JO, Green DG, Brown ES, et al. Oxygen and carbon dioxide exchange and energy cost of expired air resuscitation. J Am Med Assoc 167:328, 1958
36. Crowe DT. Managing respiration in the critical patient. Vet Med 84:55, 1989
37. Wenzel V, Idris AH, Banner MJ, et al. Exhaled gas composition of mouth to mouth ventilation during cardiopulmonary resuscitation (CPR); Abstract. Crit Care Med 22:A133, 1994
38. Ruben H, Elam JO, Ruben AM, et al. Investigation of upper airway problems in resuscitation. Anesthesiology 22:271, 1961
39. Brown DC, Lewis AJ, Criley JM. Asystole and its treatment: The possible role of the parasympathetic nervous system in cardiac arrest. J Am Coll Emerg Phys 8:448, 1979

39a. Boczar ME, Howard MA, Rivers EP, et al. A technique revisited: Hemodynamic comparison of closed- and open-chest cardiac massage during human cardiopulmonary resuscitation. Crit Care Med 23:498, 1995

40. Halperin H, Tsitlik J, Guerci A, et al. The determinants of blood flow to vital organs during cardiopulmonary resuscitation in dogs. Circulation 73:359, 1986
41. Maier GW, Tyson GS, Olsen CO, et al. The physiology of external cardiac massage: High-impulse cardiopulmonary resuscitation. Circulation 70:86, 1984

41a. von Planta I, Weil MH, von Planta M, et al. Cardiopul-

monary resuscitation in the rat (with reference to other small mammals). J Am Physiol 65:2641, 1988
42. Halpern HR, Tsitlik JE, Gelfand M, et al. A preliminary study of cardiopulmonary resuscitation by circumferential compression of the chest with use of a pneumatic vest. N Engl J Med 329:762, 1993
43. Henik RA, Wingfield WE, Angleton GM, et al. Effect of body position and ventilation/compression ratios during cardiopulmonary resuscitation in cats. Am J Vet Res 48:1603, 1987
44. Niemann JT, Rosborough JP, Niskanen RA, et al. Mechanical "cough;" cardiopulmonary resuscitation during cardiac arrest in dogs. Am J Cardiol 55:199, 1985
45. Henik RA. Basic life-support and external cardiac compression in dogs and cats. J Am Vet Med Assoc 200:1925, 1992
46. Werner JA, Greene HL, Janko CL, et al. Two-dimensional echocardiography during CPR in man: Implications regarding the mechanism of blood flow. Crit Care Med 9:375, 1981
47. Weisfeldt ML, Halperin HR. Cardiopulmonary resuscitation: Beyond cardiac massage. Circulation 74:443, 1986
48. Ewy GA, Bressler R. Cardiovascular Drugs and the Management of Heart Disease. New York, Raven Press, 1982, p 358
48a. Babbs C, Taker W, Paris R, et al. CPR with simultaneous compression and ventilation at high airway pressure in 4 animal models. Crit Care Med 10:501, 1982
49. Lippert AC, Evans AT, White BC, et al. The effect of resuscitation technique and prearrest state of oxygenation on blood-gas values during cardiopulmonary resuscitation in dogs. Vet Surg 17:283, 1988
50. Kern KB, Sanders AB, Badylak SF, et al. Long-term survival with open-chest cardiac massage after closed-chest compression in a canine preparation. Circulation 75:498, 1987
51. Heller MB. Open-chest cardiac massage. Cardiac Resusc 87:189, 1990
52. Raessler KL, Kern KB, Sanders AB, et al. Aortic and right atrial pressures during cardiopulmonary resuscitation: A potential indicator of the mechanism of blood flow. Am Heart J 115:1021, 1988
53. Sack JB, Kesselbrenner MB, Bergman D. Survival from in-hospital cardiac arrest with interposed abdominal counterpulsation during cardiopulmonary resuscitation. J Am Med Assoc 267:379, 1992
54. Crowe DT, Downs MO. Physiological effects of abdominal binding in normal and intra-abdominally bleeding dogs; Abstract. Vet Surg 15:24, 1986
55. Crowe DT, MacDonald M, Gaston J, et al. The use of a pneumatic garment in the management of hemorrhage and hypovolemic shock in dogs and cats. Scientific Proceedings, Second International Veterinary Emergency and Critical Care Symposium 2:650, 1990
56. Voorhees WD, Niebauer MJ, Babbs CF. Improved oxygen delivery during cardiopulmonary resuscitation with interposed abdominal compressions. Ann Emerg Med 12:128, 1983
57. Koehler RC, Chandra N, Guerci AD, et al. Augmentation of cerebral perfusion by simultaneous chest compression and lung inflation with abdominal binding following cardiac arrest in dogs. Circulation 67:266, 1983
58. Chandra N, Rudikoff MT, Weisfeldt ML. Simultaneous chest compression and ventilation at high airway pressures during cardiopulmonary resuscitation. Lancet 1:178, 1980
59. Wilder RJ, Weir D, Rush BF, et al. Methods of coordinating ventilation and closed cardiac massage in the dog. Surgery 53:186, 1963
60. Ditchey RB, Winkler JV, Rhodes CA. Relative lack of coronary blood flow during closed-chest resuscitation in dogs. Circulation 66:297, 1982
61. Bartlett RL, Stewart NJ Jr, Raymond J, et al. Comparative study of three methods of resuscitation: Closed-chest, open-chest manual, and direct mechanical ventricular assistance. Ann Emerg Med 13 (9 Pt 2):737, 1984
62. Sanders AB, Kern KB, Atlas M, et al. Improved resuscitation from cardiac arrest with open-chest massage. Ann Emerg Med 13:672, 1984
63. Kern KB, Sanders AB, Badylak SF, et al. Long-term survival with open-chest cardiac massage after ineffective closed-chest compression in a canine preparation. Circulation 75:498, 1987
64. Schulman AJ, Lippincott CL. Rib pivot thoracotomy. Comp Cont Educ Vet Small Anim Clin 10:927, 1988
65. Redding JS, Asuncion JS, Pearson JW. Effective routes of drug administration during cardiac arrest. Anesth Analg 46:253, 1967
66. Emerman CL, Pinchak AC, Hancock D, et al. Effect of injection site on circulation times during cardiac arrest. Crit Care Med 16:1138, 1988
67. Barsan WG, Levy RC, Weir H. Lidocaine levels during CPR: Differences after peripheral venous, central venous and intracardiac injections. Ann Emerg Med 10:73, 1981
68. Anderson J, Crowe DT. Maxillary vein cutdown. Scientific Proceedings, Second International Symposium on Veterinary Emergency and Critical Care, 1990
69. Moses BL. Cardiopulmonary resuscitation. *In* Murtaugh RJ, Kaplan PM (eds): Veterinary Emergency and Critical Care. St. Louis, Mosby–Year Book, 1992, p 508
70. Ralston SH, Tacker WA, Showen L, et al. Endotracheal versus intravenous epinephrine during electromechanical dissociation with CPR with dogs. Ann Emerg Med 14:1044, 1985
71. Roberts JR, Greenberg MI, Knaub MA, et al. Blood levels following intravenous and endotracheal epinephrine administration. J Am Coll Emerg Phys 8:53, 1979
72. Laritsky AL. Resuscitation pharmacology. *In* Chernow B (ed): The Pharmacologic Approach to the Critically Ill Patient. Baltimore, Williams & Wilkins, 1994, p 233
73. Mazkereth R, Paret G, Ezra D, et al. Epinephrine blood concentrations after peripheral bronchial versus endotracheal administration of epinephrine in dogs. Crit Care Med 20:1528, 1992
74. Hodge D, Delgondo-Paredes C, Fleisher G. Interosseous infusion flow rates in hypovolemic "pediatric" dogs. Ann Emerg Med 16:305, 1987
75. Davison R, Barresi V, Parker M, et al. Intracardiac injections during cardiopulmonary resuscitation: A low-risk procedure. J Am Med Assoc 244:1110, 1980
76. Safar P. Resuscitation in hemorrhagic shock, coma, and cardiac arrest. *In* Cowley RA, Trump BF (eds): Pathophysiology of Shock, Anoxia, and Ischemia. Baltimore, Williams & Wilkins, 1982, p 411
77. Martin D, Werman HA, Brown CG. Four case studies: High-dose epinephrine in cardiac arrest. Ann Emerg Med 19:322, 1990
78. Goetting MG, Paradis NA. High-dose epinephrine in refractory pediatric cardiac arrest. Crit Care Med 17:1258, 1989
79. Brown CG, Werman HA, Davis EA, et al. Comparative effects of graded doses of epinephrine on regional

brain blood flow during CPR in a swine model. Ann Emerg Med 15:1138, 1986
80. Brunette DD, Jameson SL. Comparison of standard versus high-dose epinephrine in the resuscitation of cardiac arrest in dogs. Ann Emerg Med 19:8, 1990
81. Stiell IG, Herbert PC, Weitzman BN, et al. High-dose epinephrine in adult cardiac arrest. N Engl J Med 327:1045, 1992
82. Ditchey RV. High-dose epinephrine does not improve the balance between myocardial oxygen supply and demand during cardiopulmonary resuscitation in dogs. J Am Coll Cardiol 3:596, 1984
83. Brillman JC, Sanders AB, Otto CW, et al. Outcome of resuscitation from fibrillatory arrest using epinephrine and phenylephrine in dogs. Crit Care Med 13:912, 1985
84. Kupersmith J, Antman EM, Hoffman BF. In vivo electrophysiological effects of lidocaine in canine acute myocardial infarction. Circ Res 36:84, 1975
85. Zipes DP. Management of cardiac arrhythmias: Pharmacological, electrical and surgical techniques. *In* Braunwald E (ed): Heart Disease. 3rd ed. Philadelphia, WB Saunders, 1988, p 621
86. Bonagura JD, Muir WW. Antiarrhythmic therapy. *In* Tilley LP (ed): Essentials of Canine and Feline Cardiology. 2nd ed. Philadelphia, Lea & Febiger, 1985, p 281
87. Singh BN, Vaughan-Williams EM. Effects of altering potassium concentration on the action of lidocaine and diphenylhydantoin on rabbit atrial and ventricular muscle. Circ Res 29:286, 1971
88. Harrison DC, Alderman EL. The pharmacology and clinical use of lidocaine as an antiarrhythmic drug. Mod Treat 9:139, 1972
89. Chadwick HS. Toxicity and resuscitation in lidocaine or bupivicaine-infused cats. Anesthesiology 63:385, 1985
90. Acheson F, Bull AB, Glees P. Electroencephalogram of the cat after intravenous injection of lidocaine and succinylcholine. Anesthesiology 17:802, 1956
91. Fox PR, Kaplan P. Feline arrhythmias. Contemp Issues Small Anim Pract 7:251, 1987
92. Fox PR. Special methods of treating arrhythmias: Cardiopulmonary arrest and resuscitation; pacemaker therapy. *In* Tilley LP (ed): Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea & Febiger, 1992, p 365
93. Kerber RE, Pandian NG, Jensen SR. Effect of lidocaine and bretylium on energy requirements for transthoracic defibrillation: Experimental studies. J Am Coll Cardiol 7:397, 1986
93a. Vukmir RB, Bircher NG, Radovsky A, Safar P. Sodium bicarbonate may improve outcome in dogs with brief or prolonged cardiac arrest. Crit Care Med 23:515, 1995
94. Weil MH, Rackow EC, Trevino R, et al. Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. N Engl J Med 315:153, 1986
95. Breslin RM, Chatterjee MB, Arieff AJ. Metabolic and hemodynamic consequences of sodium bicarbonate administration in patients with heart disease. Am J Med 87:7, 1989
96. Ng ML, Levy MN, Zieske HA. Effects of changes in pH and carbon dioxide tension on left ventricular performance. Am J Physiol 213:115, 1967
97. Weil MH, Rackow EC, Trevino R, et al. Difference in acid-base state between venous and arterial blood during CPR. N Engl J Med 315:513, 1986
98. Schweitzer P, March H. The effect of atropine on cardiac arrhythmias and conduction. Am Heart J 100:119, 1980
99. Muir WW. Effects of atropine on cardiac rate and rhythm in dogs. J Am Vet Med Assoc 172:917, 1978
100. Siesjo BK. Mechanisms of ischemic brain damage. Crit Care Med 16:954, 1988
101. Hitt ME. Oxygen-derived free radicals: Pathophysiology and implications. Compend Small Anim 10:939, 1988
102. Katz A, Reuter M. Cellular calcium and cardiac cell death. Am J Cardiol 44:188, 1979
103. Steen PA, Newberg LA, Milde JH, et al. Nimodipine improves cerebral blood flow and neurologic recovery after complete cerebral ischemia in the dog. J Cereb Blood Flow Metab 3:38, 1983
104. Capparelli EV, Hanyok JJ, Dipersio DM, et al. Diltiazem improves resuscitation from experimental ventricular fibrillation in dogs. Crit Care Med 20:1140, 1992
105. White BC, Pettinga TJ, Hoehner PJ, et al. Incidence, etiology and outcome of pulseless idioventricular rhythm treated with dexamethasone during advanced CPR. J Am Coll Emerg Phys 8:188, 1979
106. Dellinger RP, Mattox KL. Emergency resuscitation: What the books do not tell you. *In* Civetta JM, Taylor RW, Kirby RR (eds): Critical Care. Philadelphia, JB Lippincott, 1988, p 103
107. Stitzel RE, Robinson RL. Adrenomimetic drugs. *In* Craig CR, Stitzel RE (eds): Modern Pharmacology. 3rd ed. Boston, Little, Brown, 1990, p 136
108. Kerber RE, Sarnat W. Factors influencing success of ventricular defibrillation in man. Circulation 60:226, 1979
109. Yakaitis RW, Ewy GA, Otto CW, et al. Influence of time and therapy on ventricular fibrillation in dogs. Crit Care Med 8:157, 1980
110. Kerber RE, Grayzel J, Hoyt R, et al. Transthoracic resistance in human defibrillation: Influence of body weight, chest size, serial shocks, paddle size and paddle contact pressure. Circulation 63:676, 1981
111. Doherty PW, McLaughlin PR, Billingham M, et al. Cardiac damage produced by direct arrest countershock applied to the heart. Am J Cardiol 43:225, 1979
112. Befeler B. Mechanical stimulation of the heart: Its therapeutic value in tachyarrhythmias. Chest 73:832, 1978
113. Breznock EM, Kagan KG. Chemical cardioversion of electrically induced ventricular fibrillation in dogs. Am J Vet Res 39:977, 1978
114. Schertel ER, Muir WW. Shock: Pathophysiology, monitoring and therapy. *In* Kirk RW (ed): Current Veterinary Therapy. Vol X. Philadelphia, WB Saunders, 1989, p 316
115. Rush JE, Wingfield WE. Recognition and frequency of dysrhythmias during cardiopulmonary arrest. J Am Vet Med Assoc 200:1932, 1992
116. Wall RE, Rush JE. Cardiac emergencies. *In* Murtaugh RJ, Kaplan PM (eds): Veterinary Emergency and Critical Care. St. Louis, Mosby–Year Book, 1992, p 213
117. Crowe DT. Evaluation of a Doppler flow detector and probe on the eye for determining effectiveness of blood flow generation with cardiac massage in dogs. Proceedings, Third International Symposium on Veterinary Emergency and Critical Care, 1993, p 837
118. Huss BT, Anderson MA, Branson KR, et al. Evaluation of pulse oximeter probes and probe placement in healthy dogs. J Am Anim Hosp Assoc 31:9, 1995
119. Jacobson JD, Miller MW, Matthews NS, et al. Evaluation of accuracy of pulse oximetry in dogs. Am J Vet Res 53:537, 1992
120. Sidi A, Rush W, Gravenstein N, et al. Pulse oximetry fails to accurately detect low levels of arterial hemoglobin oxygen saturation in dogs. J Clin Monitor 3:257, 1987

121. Gudipati CV, Weil MH, Bisera J, et al. Expired carbon dioxide: A noninvasive monitor of cardiopulmonary resuscitation. Circulation 77:234, 1988
122. Lind B, Snyder J, Safar P. Total brain ischemia in dogs: Cerebral physiological and metabolic changes after 15 minutes of circulatory arrest. Resuscitation 4:97, 1975
123. McCord JM. Oxygen-derived free radicals in postischemic tissue injury. N Engl J Med 312:159, 1985
124. White BC, Aust SD, Arfors KE, et al. Brain injury by ischemic anoxia—Hypothesis extension. A tale of two ions? Ann Emerg Med 13:862, 1984
125. Kochanek PM, Dutka AJ, Hallenbeck JM. Indomethacin, prostacyclin and heparin improve post-ischemic cerebral blood flow without affecting early post-ischemic granulocyte accumulation. Stroke 18:634, 1987
126. Safar P. Cardiopulmonary-cerebral resuscitation. *In* Shoemaker WC, Ayres S, Grenvik A, et al (eds): Textbook of Critical Care. 2nd ed. Philadelphia, WB Saunders, 1989, p 5

22

Syncope and Episodic Weakness

JOHN E. RUSH

Syncope is a sudden, transient loss of consciousness with spontaneous recovery. Episodic weakness, near-syncope, and presyncope represent less severe grades of syncope characterized by sudden generalized muscle weakness, rear limb weakness, ataxia, or collapse. Syncope should not be thought of as a clinical entity, but rather as a sign of an underlying disease.

CAUSES AND CLINICAL SIGNIFICANCE

The cause of syncope should be aggressively pursued because underlying disorders are often severe or potentially lethal. Causes range from benign conditions to life-threatening arrhythmias and fall into one or more of four major pathophysiologic categories: (1) cardiogenic dysfunction, (2) hypotensive disorders, (3) alterations in blood constituents, and (4) neurologic causes. It is important to consider causes other than structural cardiovascular disease in cases of syncope. In three large human studies, cardiovascular disease was established as the cause in only 13 percent of patients.[1-3] Diagnosis, however, is often elusive. Although no comparable data exist for animals, the cause of syncope in up to 40 percent of humans is never identified.[4]

CARDIOGENIC SYNCOPE

Common causes of this category include bradyarrhythmias (e.g., advanced heart block, severe sinus bradycardia, sick sinus syndrome); supraventricular or ventricular tachycardias; cardiac underfilling (e.g., cardiac tamponade, large space-occupying intracardiac masses); and reduced ventricular ejection (e.g., aortic or pulmonic stenosis, hypertrophic obstructive cardiomyopathy, severe intravascular volume depletion).

HYPOTENSIVE SYNCOPE

Hypotension is often the cause of episodic weakness or presyncope, and it can cause syncope in some animals. It may result from inadequate cardiac performance, decreased blood volume, or diminished vascular tone. Inadequate cardiac pump function in dilated cardiomyopathy can result in hypotension and syncope. Causes of hypovolemia include external, internal, or gastrointestinal blood loss, excessive diuresis, diarrhea, hypoadrenocorticism, and diseases that lead to fluid loss. Hypotensive weakness must be considered in animals receiving cardiac drug therapy, especially vasodilators and β-adrenergic blocking drugs.

SYNCOPE FROM ALTERED BLOOD CONSTITUENTS

Less common causes of syncope include hypoglycemia, hypoxia, severe anemia, and hyperviscosity syndromes. The brain has very limited storage of high-energy phosphates for oxidative phosphorylation and requires continuous delivery of both oxygen and glucose for normal function.

NEUROGENIC SYNCOPE

Diseases that cause obstruction to cerebral blood flow, such as thromboembolism and arteriosclerosis, can also cause syncope. Cessation of blood flow for as little as 7 to 10 seconds can lead to loss of consciousness. Prevailing systemic, metabolic, or cardiovascular diseases can worsen this condition.

CLINICAL APPROACH TO THE SYNCOPAL PATIENT

The goals of evaluation are to (1) establish a diagnosis, (2) define related and contributory factors, (3) assess the risk related to future events, (4) determine the need for therapy, and (5) establish a prognosis. Because of the transient nature of syncope, most pets are asymptomatic at the time of clinical examination.

A complete physical examination must be performed. In my practice, over 50 percent of syncope cases were diagnosed following initial history, physical examination, 10-lead electrocardiogram (ECG), and thoracic radiographs. The ECG should include a lead II rhythm strip for at least 5 minutes.

Additional testing may be required. Clinical pathology may provide additional useful information, including a complete blood count, serum biochemistry profile (including glucose and potassium levels), and urinalysis. Evaluation of the stool for occult blood may identify patients with hypovolemia resulting from gastrointestinal bleeding. Echocardiography should be performed when a cardiovascular cause is suspected or when routine testing fails to identify a cause of syncope. Blood pressure measurement is useful in animals receiving cardiovascular active drugs. If clinically indicated and available, serum drug concentrations should be assessed. Abdominal radiographs and diagnostic ultrasound are helpful to detect abdominal masses, especially in elderly or large-breed dogs such as German shepherds and golden retrievers with episodic weakness due to bleeding tumors.

DIFFERENTIATION OF SYNCOPE AND SEIZURES

HISTORY

A careful history should include a complete and detailed description of the "event" to help differentiate seizures from syncopal episodes. Syncope, collapse, and seizures are common clinical presentations for a variety of diseases (Table 22–1). Historical data that favor a diagnosis of syncope over seizures are concurrent cardiac disease; precipitation of syncope by coughing, excitement, or exercise; history of severe cardiac arrhythmias; syncope or sudden death in related animals; and vasodilator or β-adrenergic blocking drug therapy. Lack of response to anticonvulsant therapies or episodes of increasing frequency despite initiation of anticonvulsant drugs favor a diagnosis of syncope.

Teaching the pet owner how to observe and record future abnormal occurrences is often helpful. This must include the observations of the pet's "event," associated behavior, and circumstances. Many clients can be taught how to take an accurate pulse rate or heart rate with an inexpensive stethoscope.

TABLE 22–1
Differential Diagnoses for Syncope and Episodic Weakness

- Primary cardiac causes (see Table 22–2)
  - Arrhythmias
  - Obstruction to cardiac filling
  - Obstruction of ventricular ejection
- Hypotension
  - Inadequate cardiac output (e.g., dilated cardiomyopathy, tachy/bradyarrhythmia)
  - Inadequate vascular tone (e.g., vasodilators, β-blockers)
  - Inadequate blood volume
    - Blood loss
      - Internal (e.g., splenic hemangiosarcoma, GI blood loss)
      - External (e.g., trauma)
    - Diuresis (e.g., furosemide)
    - Hypoadrenocorticism
    - Fluid loss (e.g., emesis, diarrhea)
- Hypoxemia (e.g., respiratory failure, pulmonary thromboembolism)
- Abnormalities of blood constituents
  - Hypoglycemia
  - Hypokalemia
  - Anemia
  - Hepatoencephalopathy
- Neurologic and neuromuscular disorders
  - Epilepsy
  - Structural CNS disorders
    - Neoplasia
    - Cerebral arterial disease
    - Thromboembolism
  - Narcolepsy
  - Myasthenia gravis

CLINICAL OBSERVATION

Observable components of a classic seizure include (1) a preictal period, (2) an ictus or seizure event composed of tonic/clonic limb motions and, frequently, motor activity, chomping, and hypersalivation, and (3) a postictal period of variable duration (commonly 10 minutes or longer). Involuntary urination and defecation can occur with either seizure or syncope.

Components of a classic syncopal episode include collapse and transient loss of consciousness. Infrequently, affected animals may display an outward indication of impending collapse, such as acute weakness, staggering, or vocalization. Compared with animals with seizures, syncopal patients are more likely to extend their head back into a position of opisthotonos. The animal in syncope is often motionless; skeletal muscles may be relaxed or the limbs may be rigidly extended. Subsequently, struggling to rise can occur during recovery from the episode. This is often frantic, is somewhat uncoordinated, and can be confused with tonic/clonic limb motions. Many syncopal animals have normal mentation immediately following the syncopal event, compared with the blunted mentation typical of postictal seizure behavior. Most syncopal animals are able to walk normally within a few minutes after the syncopal event. Facial chomping and hypersalivation are rarely noted in syncopal pets.

The duration of the "event" may be useful in differentiating seizures from syncope. Seizures have a variable duration, but the actual ictus often lasts 1 to 2 minutes. In small-breed dogs with endocardiosis and coughing, and in cats with hypertrophic cardiomyopathy, the syncopal episode may last for only a few seconds. Many are then able to stand within 1 minute. Alternatively, syncopal episodes may last much longer in large-breed dogs, pets with prolonged ventricular arrhythmias, and disorders causing obstruction to blood flow. Five to 15 minutes may elapse until the animals are strong enough to rise. In animals with hypovolemia or drug-induced weakness, the duration of the event is quite variable, but it may last for minutes to hours.

Identification of underlying diseases may help differentiate syncope from seizures. Most metabolic causes of seizures and weakness (i.e., hypoglycemia, hepatic failure, anemia, hypokalemia) can be determined by routine diagnostic tests, especially when clinical signs are manifested. If neurologic deficits are present, cardiovascular syncope is unlikely.

In some cases, the cause of the event is still unclear after soliciting a careful history, performing a clinical examination, and initial testing. It should be recognized that generalized clonic movements may occur with any condition that results in severe hypotension and pancerebral hypoperfusion. Differentiation of syncope from a true seizure can be difficult in these situations.

SPECIALIZED TESTING

Continuous Ambulatory ECG (Holter Monitor) Recording

The use of intermittent, short-duration ECG rhythm strips to intercept transient arrhythmias is highly unreliable. Holter monitor recording, or continuous ambulatory ECG recording, can be used to search for arrhythmic causes of syncope (see also chapter 18). The optimal duration of Holter monitoring is not known. However, it is generally accepted that 24 hours of ECG monitoring increases the overall detection of arrhythmias when compared with 12 hours. The Holter monitor is attached to the patient and the ECG is recorded on a tape for subsequent analysis. As the duration of the recording is only 24 hours, syncopal events that occur infrequently may not be identified. If the syncopal event occurs during the recording period spontaneously or when precipitated by exercise or excitement, this diagnostic test can be highly useful (Fig. 22–1).

Holter recording may yield positive, negative, or inconclusive findings. Results are positive when syncope occurs at the time of a hemodynamically significant arrhythmia, in which case the arrhythmia is implicated as the cause for the event. Negative results occur when the recorded ECG is normal at the time of the collapsing episode. In this case, causative cardiac arrhythmia can be excluded. Often, the animal does not collapse or have a syncopal episode during the recording period and the Holter monitoring recordings contain no suspicious arrhythmias.

In certain cases, cardiac arrhythmias known to be associated with collapse (i.e., ventricular tachycardia or advanced atrioventricular block) are identified by Holter monitoring but were not hemodynamically severe enough to have resulted in collapse. Despite a lack of temporal association, the arrhythmia is often presumed to be causative, and suppressive antiarrhythmic therapy is instituted (chapters 17 to 19). When structural heart disease is present, runs of ventricular tachycardia during Holter monitor recording may have greater clinical significance than ventricular arrhythmias recorded in animals having normal cardiac structure and function. Ventricular arrhythmias may be more significant when recorded in Doberman pinschers and boxers with cardiomyopathy or myocarditis (chapter 27).

In a study evaluating a large number of syncopal humans, Holter monitor recording had a low diagnostic yield.[5] Similar studies are not available for animals, although in my experience, definitive diagnostic find-

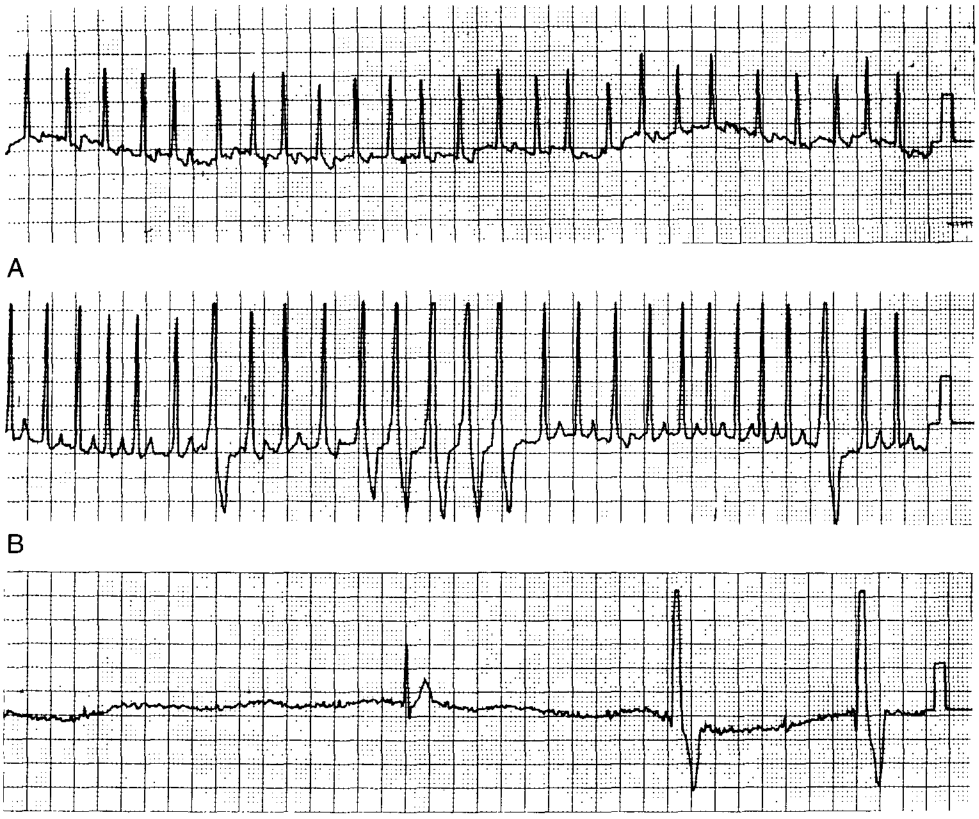


FIGURE 22–1

Holter monitor recordings from a dog with dilated cardiomyopathy and episodic weakness. Medications included digoxin, furosemide, captopril, and diltiazem. (A) Atrial fibrillation at 200 beats/min. (B) Atrial fibrillation with ventricular arrhythmias. Weakness was not evident at the time of this recording. (C) ECG recording at the time of weakness, 40 minutes after diltiazem administration, shows atrial fibrillation with profound bradycardia, presumably due to advanced AV block. One junctional beat and two ventricular escapes are identified. Episodic weakness resolved with discontinuation of diltiazem. Paper speed, 25 mm/sec; 1 cm = 1 mV.

ings should be expected in no more than 15 to 20 percent of Holter recordings.

In-Hospital ECG Monitoring

Electrocardiographic monitoring during hospitalization may permit identification of arrhythmias responsible for syncope or episodic weakness. Continuous ECG monitoring is useful in selected patients, either in combination with or as a substitute for Holter monitor recording. Continuous monitoring may be performed using telemetric ECG recordings or hard-wire recordings in which the patient is directly connected to the electrocardiograph. If continuous monitoring is not possible, serial ECGs recorded every 2 to 4 hours may help identify some transient arrhythmias.

Exercise ECG Testing

In some cases, exercise may provoke arrhythmia or syncope, and ECG monitoring may document the event. There are no standardized regimens for exercise ECG testing in small animals. Because cats rarely cooperate with exercise, the technique is used almost exclusively in canines. Dogs are usually exercised on a treadmill or in an open area. Exercise testing is terminated if the patient collapses or when significant arrhythmia is identified. In many instances, none of these endpoints are reached.

Exercise stress testing may be especially useful in evaluation of dogs who manifest clinical signs with exertion or excitement. The lack of an appropriate increase in heart rate in response to exercise may point to sinus node dysfunction in patients with unexplained bradycardia. Development of exercise-induced AV block at low heart rate suggests disease in the distal portions of the conduction system. Supraventricular and ventricular tachyarrhythmias may also be provoked by exercise. It has been hypothesized that ventricular tachycardias precipitated by exercise may reflect a catecholamine sensitivity, implying that β-blockade may be useful. In people, exercise testing is considered diagnostically inferior to Holter monitoring, although in selected individuals this test may be preferred.[6]

Vagal Maneuver or Other Provocative Testing

If identifiable circumstances or provocations can produce significant arrhythmias or collapse, these activities should be performed during ECG monitoring. Coughing or excitement can precipitate collapse in some small-breed dogs, and tracheal stimulation during ECG monitoring may incite arrhythmia and syncope. In others, vagal maneuvers performed during ECG monitoring may demonstrate exaggerated vagal

response with marked bradycardia, sinus arrest, or AV block.

Carotid sinus massage is performed with the head extended and turned slightly away from the side to be massaged (chapters 18 and 19). The carotid sinus is located just caudal to the angle of the mandible and dorsal to the trachea. This region is compressed upward against the vertebral bodies and is repeatedly massaged in a cranial-to-caudal direction. If a vagal maneuver produces profound bradycardia in a pet with syncope, a therapeutic trial with anticholinergic drugs may be attempted.

Another proposed provocation during ECG testing is partial airway obstruction. Susceptible individuals may increase inspiratory effort, which may result in a reflex-induced bradycardia.

Signal-Averaged ECG, Upright Tilt Testing, and Electrophysiologic Testing

These specialized techniques are used to evaluate people with syncope but have had little exposure in clinical veterinary medicine. Signal-averaged electrocardiography has identified people who are likely to have ventricular tachycardia as the cause of syncope.[7] Upright tilt testing is used to evaluate humans for vasovagal or vasodepressor syncope. When tilted at a 70° angle for up to 15 minutes, patients predisposed to vasovagal syncope will experience syncope or presyncope.[8] Electrophysiologic testing involves cardiac catheterization to induce arrhythmias and record intracardiac electrograms. The diagnostic yield appears to be highest in humans with underlying structural heart disease or coronary artery disease.[9]

MANAGEMENT OF SYNCOPE

CARDIOGENIC SYNCOPE

Arrhythmias

Arrhythmias are important causes of syncope in dogs and cats. Bradycardia associated with advanced forms of atrioventricular block is a recognized cause of feline syncope.[10, 11] In cats with hypertrophic obstructive cardiomyopathy, syncope or episodic weakness can accompany activity, which usually increases heart rate and dynamic left ventricular outflow tract obstruction (Fox PR, personal communication). In dogs, tachycardia-induced syncope is observed with some frequency. It is typically associated with ventricular arrhythmias, although atrial fibrillation and supraventricular tachycardia can also cause syncope or episodic weakness. High-grade second-degree and complete atrioventricular block and sick sinus syndrome account for most bradyarrhythmias resulting in syncope.[12] Asystole and severe sinus bradycardia can result in collapse. Arrhythmia management is discussed in detail in chapters 17 to 19.

TACHYARRHYTHMIAS. Syncope resulting from ventricular or supraventricular tachyarrhythmia is usually associated with significant underlying cardiac disease or severe extracardiac disorders. Affected animals should always have a thorough evaluation, including radiographic and echocardiographic examinations and appropriate clinical pathology testing. Dilated cardiomyopathy and chronic acquired valve disease are the most common causes of canine tachyarrhythmias. Syncope frequently accompanies concurrent congestive heart failure. In cats, tachyarrhythmias are usually associated with hypertrophic and restrictive cardiomyopathy or hyperthyroidism.

Hemodynamically and electrically unstable tachyarrhythmias often result from severe extracardiac diseases. Hemangiosarcoma involving the right atrium is a common cause of ventricular tachycardia in large-breed older dogs. Other neoplasia may also invade the heart, especially lymphoma in the cat. Systemic and metabolic disorders, sepsis, and coagulopathies may cause myocardial structural or functional changes and arrhythmias (chapter 33). Therapy is directed at both arrhythmia suppression and the underlying disorder.

The prognosis for animals with syncope due to tachyarrhythmias is related to the type and degree of underlying disease. Ventricular arrhythmias are much more likely to result in sudden death than supraventricular arrhythmias, and for this reason they should be aggressively treated. In one human study,[3] the overall 1-year mortality rate for patients with cardiovascular cause for syncope was 30 percent. The subgroup with the highest risk had advanced atrioventricular block or ventricular tachycardia. Especially with ventricular tachycardia, syncope is often an antecedent to sudden death.[13] Although the therapeutic end-point of antiarrhythmic therapy is a matter of debate, effective management should be directed to alleviate syncope and reduce the likelihood of sudden death (chapters 17 to 19).

SICK SINUS SYNDROME. This condition causes sinus slowing, sinus arrest, and supraventricular tachycardia (Fig. 6–36). A form of sick sinus syndrome—the bradytachy syndrome—is present when extended intervals of asystole without escape beats are punctuated by supraventricular tachycardia. Most affected dogs are symptomatic during these intervals of prolonged bradycardia. Pacemaker implantation prevents further episodes of syncope. Sick sinus syndrome rarely can be managed with oral anticholinergics (e.g., propantheline, 0.25 mg/kg tid), β-adrenergic drugs (e.g., terbutaline, 0.25 to 1.0 mg/kg tid) or theophylline (e.g., aminophylline, 6 to 10 mg/kg tid). When pacemaker implantation is not possible, the likelihood for recur-

rent syncope is high, although sudden death is uncommon.

BRADYARRHYTHMIAS. High-grade second-degree AV block and complete (3°) AV block commonly results in symptomatic bradycardia and syncope in dogs and cats. Most symptomatic pets have advanced AV block on their resting ECG. However, some may only have mild AV block, with or without accompanying conduction system abnormalities (i.e., bundle branch block or fascicular block). Occasionally, long intervals of normal conduction occur. The arrhythmia may represent a manifestation of widespread cardiac disease such as cardiomyopathy or myocarditis. Pacemaker implantation is indicated for advanced AV block and usually abolishes syncope (chapter 20). The prognosis without pacemaker implantation is guarded, and sudden death is common.

Structural Cardiac Diseases

Common cardiac diseases associated with syncope include aortic stenosis, pulmonic stenosis, dilated cardiomyopathy, advanced chronic acquired valvular disease, hypertrophic cardiomyopathy, cardiac neoplasia, and pericardial effusion (Table 22–2). Pulmonary embolism and pulmonary hypertension, with or without heartworm disease, can also cause syncope.

OBSTRUCTION TO FORWARD BLOOD FLOW. With severe cardiac outflow obstruction from aortic or pulmonic valve stenosis, exercise may precipitate syncope when forward cardiac output is impeded. Hypertrophic cardiomyopathy may cause dynamic obstruction to the left ventricular outflow tract secondary to ventricular septal hypertrophy and abnormal anterior mitral valve motion (i.e., hypertrophic obstructive cardiomyopathy), although inadequate coronary circulation or arrhythmias may also contribute (chapter 28).

HEART FAILURE. Although not a disease *per se*, heart failure results from a variety of structural or functional cardiac derangements. Syncope often occurs with the onset of cardiac decompensation and thus serves as a clinically useful marker of congestive heart failure. Dogs with dilated cardiomyopathy or chronic valvular disease can collapse when cardiac output is decreased by myocardial failure, valvular regurgitation, or tachycardia, especially when combined with coughing (see tussive syncope later). Overzealous diuresis or hypotension caused by vasodilator drugs may be contributory. The prognosis is better for collapse associated with heart failure than for syncope resulting from ventricular arrhythmias.

VENTRICULAR UNDERFILLING. Intracardiac mass lesions may reduce ventricular filling by obstructing blood flow through atrioventricular valves, by obstructing the right ventricular outflow tract, or interfering with blood returning from systemic or pulmonic veins. Car-

TABLE 22–2
Cardiovascular Causes of Syncope and Breed Predispositions

Causes of Syncope	*Breed Predispositions**
Structural Heart Diseases	
Dilated cardiomyopathy	Doberman pinscher, boxer, cocker spaniel, giant-breed dogs
Chronic valvular disease	Small-breed dogs (middle-aged to geriatric)
Pulmonic stenosis	English bulldog, Samoyed, beagle, Chihuahua, cocker spaniel, others
Aortic stenosis	Newfoundland, boxer, golden retriever, German shepherd, others
Right-to-left shunting congenital defects	English bulldog
Hypertrophic cardiomyopathy	Cats (Maine coon, Himalayan); German shorthair pointer
Pericardial effusion	German shepherd, golden retriever, others
Intracardiac mass lesions (neoplasia; thrombus)	
Cardiac Arrhythmias	
Sick sinus syndrome	Miniature schnauzer, dachshund
Advanced AV block	German shepherd, dachshund, pug, Doberman pinscher
Asystole	
Sinus bradycardia	
Supraventricular tachycardia	Labrador retriever
Ventricular tachycardia	German shepherd, boxer, Doberman pinscher
Cor Pulmonale	
Pulmonary embolism	
Pulmonary hypertension	
Heartworm disease	
Tussive "Cough Drop" Syncope	Small-breed dogs with combined cardiopulmonary disease
Vasovagal Syncope	Boxer, brachycephalic breeds?

*Does not exclude other breeds from being affected.

diac tamponade is the most common cause of ventricular underfilling (chapter 29) and is commonly associated with ventricular arrhythmias in dogs. Episodic weakness from lack of forward cardiac output is a common clinical complaint. The prognosis is largely dependent upon etiology.

Vasovagal and Related Reflex Causes of Syncope

This category includes vasovagal syncope and other recognized or proposed etiologies resulting from inappropriate autonomic reflex responses, including carotid sinus hypersensitivity, postural hypotension, and syncope induced by micturition, defecation, or hyperventilation.

VASOVAGAL (NEUROCARDIOGENIC) SYNCOPE. In humans, vasovagal syncope is the most common identifiable cause of syncope. The term "neurocardiogenic syncope" has replaced "vasovagal syncope." Neurocardiogenic syncope is the result of counterproductive reflexes that defeat the normal vascular responses needed to maintain blood pressure.[14] Hypotension or hypovolemia are precipitating events. In a normal individual, hypotension or hypovolemia is counteracted by increases in adrenergic sympathetic tone and diminished parasympathetic tone. In susceptible patients, syncope occurs when there is a sudden withdrawal of sympathetic tone and an increase in parasympathetic activity. This results in a precipitous drop in vasomotor tone at the same time as decreasing heart rate. It is this paradoxic interruption of the normal responses to hypovolemia that causes syncope. This abnormal reflex appears to occur in response to cardiac mechanoreceptor stimulation. The initial adrenergic stimulation in response to hypovolemia leads to vigorous contraction of a relatively empty ventricle. This stimulus to myocardial mechanoreceptors, or C fibers, results in inhibition of sympathetic tone and increases parasympathetic efferent activity. The overall consequences of these reflexes are hypotension and bradycardia, and the resulting decrease in cerebral blood flow causes syncope.

In most patients, both components of the abnormal reflex are active, although in a given individual one component may predominate. Therefore, in any given patient, either the vasodepressor aspect or the bradycardic aspects may be primarily responsible for symptoms. Studies in animals and in people have documented that alleviation of the bradycardic limb of the reflex with atropine or cardiac pacing fails to prevent the occurrence of syncope.

Vasovagal syncope can occur in normal healthy animals or in animals with systemic disease. Boxers have been described with a syndrome that resembles vasovagal syncope.[15] Individual animals may have a predisposition to develop vasovagal syncope, and the additional stress of another disease process can increase the frequency of syncopal events. Dehydration, hypovolemia, and certain drugs are recognized to lead to its development.

Vasodepressor syncope may be managed with either anticholinergic drugs (e.g., propantheline, 0.25 to 1.0 mg/kg tid) or β-blocking drugs (e.g., metoprolol, 0.2 to 1 mg/kg tid). Anticholinergic drugs act to prevent the reflex cardiac slowing, but as previously described, this may be inadequate treatment to prevent syncope; β-adrenergic blockers work earlier in the reflex arc to prevent the initial release of catecholamines. In addition, β-blockers have a blocking effect on cardiac mechano-receptors. Disopyramide is reported to be an effective treatment in people with neurocardiogenic syncope. I have managed several young boxers with a syndrome that resembles neurocardiogenic syncope. Although a definitive diagnosis was not confirmed, frequent syncope has been well controlled for several years with metoprolol (0.2 to 1 mg/kg bid to tid), a β_1-specific β-blocker. The prognosis with neurocardiogenic syncope is good; although recurrent syncope is possible, sudden death is unlikely.

CAROTID SINUS HYPERSENSITIVITY. This is an uncommon cause of syncope. Stimulation of the carotid sinus sends afferent impulses to the vasomotor center of the brain. Increased vagal tone leads to bradycardia, whereas diminished vasomotor tone results from inhibition of the sympathetic nervous system. This syndrome has been reported in humans with neoplasia and inflammatory processes in the neck.

ADDITIONAL CAUSES OF REFLEX SYNCOPE. In humans, these include postural hypotension, hyperventilation, and syncope during or following micturition or defecation. Postural hypotension results from inadequate increase in vascular tone when rising from recumbency. Volume depletion and cardiac medications may contribute to this problem. Oropharyngeal stimulation, gastric distention, and capsular pressure resulting from swelling of internal organs may also initiate reflexes that result in syncope. Hyperventilation is reported to lead to syncope via hypocapnia, which causes cerebral arterial vasoconstriction. The final types of reflex-mediated syncope are those that occur at the time of, or immediately following, micturition or defecation.

CENTRAL NERVOUS SYSTEM CAUSES OF SYNCOPE

Neurologic etiologies are rarely proved as the cause of syncope in animals. It is often difficult to differentiate seizures from syncope. The central nervous system modulates both excitatory and inhibitory influences

on autonomic discharge and can directly or indirectly influence blood pressure, arterial tone, and cardiac rate and rhythm. The relationship between the brain and the heart is important to consider in animals with severe or multiple seizures, those with brain trauma, and those with intracranial bleeding disorders. In these cases seizures, syncope, or both may occur. Several studies have documented the association between cardiac arrhythmias and neurologic disorders.[16, 17] Electrocardiographic changes in humans with neurologic disease may include prolongation of the QT interval, ST-segment depression, and non-specific T wave changes.[16] Bradyarrhythmias and tachyarrhythmias have also been recognized in these cases, and postmortem examinations have demonstrated myocardial damage. Seizures may occur in association with cardiac arrhythmias in either a cause or effect relationship. In the latter, seizures may result from poor central nervous system perfusion following frequent or prolonged syncopal episodes. Syncope caused by diminished cerebral blood flow secondary to intracerebral vascular disorders is uncommon in veterinary medicine.

TUSSIVE SYNCOPE ("COUGH DROP" SYNCOPE)

Tussive, or "cough drop," syncope is one of the most common causes of syncope in dogs. It typically occurs in small breeds and is associated with collapsing trachea, chronic obstructive pulmonary disease, brachycephalic syndrome, and chronic acquired valve disease (endocardiosis).

Syncope most commonly occurs during or immediately after coughing. In some cases owners will describe a different precipitating activity, such as gagging, an attempt to vomit or retching, a hard or forceful swallow, or an acute episode of excitement coupled with heightened respiratory activity. Multiple episodes of syncope are common.

Several mechanisms have been proposed to explain syncope associated with coughing. Cerebral blood flow may be decreased as a result of increased intracranial pressure during paroxysms of coughing. Paroxysmal coughing may increase intrathoracic pressure, which results in diminished cardiac venous return and attendant decreases in cardiac output. Reflex cardiac slowing and/or peripheral vasodilation (similar to neurocardiogenic syncope) may be triggered by coughing and lead to collapse. Alternatively, cardiac tachyarrhythmias may be precipitated by coughing and contribute to collapse.

Management includes therapies directed at the underlying respiratory and cardiac diseases, including antitussive medications (hydrocodone, 0.22 mg/kg bid to tid; butorphanol, 0.5–1 mg/kg bid to qid) and bronchodilators (aminophylline, 10 mg/kg tid; theophylline sustained-release, 20 mg/kg od to bid). Respiratory disease may be better defined and specifically treated following bronchoscopy with tracheal cytology and culture. Management of heart disease will help alleviate coughing resulting from heart failure. However, coughing resulting from compression of main airways by an enlarged left atrium may persist regardless of therapy. The outcome is usually related to the prognosis for the underlying disorder, as few dogs die as a result of tussive syncope. Recurrent syncopal events are common, especially with cardiac decompensation.

DRUG-RELATED SYNCOPE

Many drugs can cause or contribute to syncope. Calcium channel blockers and β-adrenergic blockers, particularly at toxic doses or in combination therapy, can cause a precipitous drop in heart rate and/or cause AV block. Other drugs such as vasodilators, nitrates, β-adrenergic blockers, or calcium channel blockers, which affect vascular tone, can cause hypotension, weakness and syncope. Diuretics can contribute, owing to potential blood volume contraction and electrolyte depletion.

It is often difficult to determine whether syncope results from drug administration or from cardiac disease and arrhythmia. If drug toxicity is suspected, one must reaffirm the correct dose, determine whether client compliance is accurate, assess for systemic or metabolic causes that could alter drug elimination, and assay for serum drug concentrations when possible (e.g., digitalis glycosides). In pets receiving polypharmacy, the diuretic dose is typically reduced, assuming other steps have been evaluated. Alterations in the types or doses of other medications is attempted if this step fails.

UNKNOWN CAUSES OF SYNCOPE

No definitive etiology can be established in a large number of syncopal animals. In many, the rate of recurrence is low. There seems to be a low incidence of sudden death in human patients who were extensively studied and who have no identifiable cause of syncope,[3, 18] although no similar studies have been reported in animals.

REFERENCES

1. Martin GJ, Adams SL, Martin HG, et al. Prospective evaluation of syncope. Ann Emerg Med 13:499, 1984

2. Eagle KA, Black HR, Cook EF, et al. Evaluation of prognostic classifications for patients with syncope. Am J Med 79:455, 1985
3. Kapoor WM, Carpe M, Wiegand J, et al. A prospective evaluation and follow up of patients with syncope. N Engl J Med 309:197, 1983
4. Eagle KA, Pruitt AA. Syncope. *In* Eagle KA, Haber E, DeSanctis RW, Austen GW (eds): The Practice of Cardiology. 2nd ed. Boston, Little, Brown, 1989, p 45
5. Gibson JC, Heitzman MR. Diagnostic efficacy of 24-hour electrocardiographic monitoring for syncope. Am J Cardiol 53:1013, 1984
6. Brooks R, Garan H, Ruskin JN. Evaluation of the patient with unexplained syncope. *In* Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, WB Saunders, 1990, p 646
7. Winters SL, Steward D, Gomes JA. Signal averaging of the surface QRS complex predicts inducibility of ventricular tachycardia in patients with syncope of unknown origin: A prospective study. J Am Coll Cardiol 10:775, 1987
8. Sra JS, Anderson AJ, Sheikh SH, et al. Unexplained syncope evaluated by electrophysiologic studies and head-up tilt testing. Ann Intern Med 114:1013, 1991
9. Ruskin JN, Schoenfeld MH. Mechanisms of ventricular arrhythmias. *In* Eagle KA, Haber E, DeSanctis RW, Austen GW (eds): The Practice of Cardiology. 2nd ed. Boston, Little, Brown, 1989, p 207
10. Stamoulis ME, Bond BR, Fox PR. Pacemaker therapy for symptomatic bradycardia in the cat. J Vet Emerg Crit Care 2:67, 1992
11. Fox PR, Moise NS, Woodfield J, Darke PGG. Techniques and complications of pacemaker implantation in four cats. J Am Vet Med Assoc 199:1742, 1991
12. Fox PR, Matthiesen DT, Purse D, Brown NO. Ventral abdominal trans-diaphragmatic approach for implantation of cardiac pacemakers in the dog. J Am Vet Med Assoc 189:1303, 1986
13. Kramer MR, Drori Y, Lev B. Sudden death in young soldiers: High incidence of syncope prior to death. Chest 93:345, 1988
14. Sra JS, Jazayeri MR, Avitall B, et al. Comparison of cardiac pacing with drug therapy in the treatment of neurocardiogenic syncope with bradycardia or asystole. N Engl J Med 328:1085, 1993
15. Fischer EW. Fainting in Boxers—the possibility of vasovagal syncope (Adams-Stokes attacks). J Small Anim Pract 12:347, 1971
16. Samules MA. Electrocardiographic manifestations of neurologic disease. Semin Neurol 4:453, 1984
17. Oppenheimer SM, Cechetto DF, Hachinski VC. Cerebrogenic cardiac arrhythmias. Arch Neurol 47:513, 1990
18. Eagle KA, Black HR. The impact of diagnostic tests in evaluating patients with syncope. Yale J Biol Med 56:1, 1983

V

Diseases of the Heart and Circulation

23

Prevalence of Cardiovascular Disorders

JAMES W. BUCHANAN

Knowledge of cardiovascular disease prevalence aids in developing differential diagnoses and constitutes an important aspect of cardiovascular epidemiology.[1] Disease occurrence, frequency, and breed predilections may change over time, as is evident in trends reported in 1992[1] and 1968.[2] This chapter adds epidemiologic insights to congenital and acquired heart disease. Additional information is contained in chapters covering specific diseases.

CARDIOVASCULAR DISEASE PREVALENCE

CANINE

Types and prevalence of canine heart disease were first characterized 30 years ago in a survey of 5000 dogs presented to the Veterinary Hospital of the University of Pennsylvania.[3] Eleven percent had reliable signs of heart disease, and another 9 percent had possible heart disease. Since the incidence of heartworm disease is low in this region, the frequency of heart disease could actually be greater in endemic heartworm regions. A similar prevalence study of 4325 dogs recently conducted at the Animal Medical Center in New York City disclosed cardiovascular disease in 483 dogs (11%) (Fox PR, Pipers F, unpublished data). In 1988, heart disease was reported in 11 percent of 7148 dogs surveyed in Italy.[4]

To determine whether disease epidemiology has changed in dogs in the Philadelphia area, the types and relative frequency of heart disease were surveyed from 1990 to 1993 in 300 dogs that had reliable clinical signs of heart disease (Table 23–1). The most common types of acquired heart diseases are chronic acquired atrioventricular valvular disease, cardiomyopathy, and pericardial effusion secondary to neoplasia.

In comparison with data reported in 1968,[2] some notable differences were recorded in the relative disease frequency and breed. This may be due in part to changes in breed popularity, as well as increased disease incidence in certain breeds, and improved diagnostic methods. Differences also reflect a greater proportion of referred patients with congenital heart disease, as well as animals with acute heart failure presented to our busy emergency service. The types and relative frequency of arrhythmias in these dogs are listed in Table 23–2. It is interesting that cardiovascular disorders tabulated from 813 dogs examined at a cardiology clinic in Milan, Italy,[5] are relatively similar in type and frequency to those recorded in Table 23–1.

TABLE 23–1
Cardiac Diseases in 300 Dogs*

Diagnosis	Number	%
Chronic valvular disease (33 also had arrhythmias)	120	40.0
Primary arrhythmia (shortening fraction > 25%)	50	16.7
Congenital heart disease (4 also had arrhythmias)	49	16.4
Dilated cardiomyopathy (24 also had arrhythmias)	34	11.3
Pericardial effusion (12 had visible mass; 5 had arrhythmias)	21	7.0
Neoplasm without pericardial effusion (6 had arrhythmias)	9	3.0
Heartworms	7	2.3
Other (3 had arrhythmias)	10	3.3
TOTAL	300	100.0
Congestive heart failure	106	35.3

*All dogs with reliable signs of heart disease and owner's last name beginning with A–F. From the 1990–1993 files of The Veterinary Hospital, University of Pennsylvania, Cardiology Section. Approximately 1-year case load, excluding all cats, normal dogs, and dogs with signs of possible heart disease.

TABLE 23–3
Frequency of Cardiopulmonary Disease in 500 Cats*

Diagnosis	Number	%
Hypertrophic cardiomyopathy	118	22.5
Intermediate cardiomyopathy	81	15.5
Mitral insufficiency, unknown cause	75	14.3
Dilated cardiomyopathy	65	12.4
Hyperthyroidism	51	9.8
Congenital heart disease	34	6.5
Myocardial disease, other	22	4.2
Pleural effusion, noncardiac	20	3.8
Systemic thromboembolism	18	3.4
Primary pulmonary disease	11	2.1
Pericardial disease	11	2.1
Systemic hypertension	6	1.1
No diagnosis	12	2.3
TOTAL	524	100.0
Congestive heart failure	103	20.6

*Angell Memorial Animal Hospital, 1985 to 1989.
Adapted from Harpster NK. Feline arrhythmias: Diagnosis and management. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 732.

FELINE

The overall frequency of feline cardiovascular disease assessed by clinical evaluation has not been surveyed as thoroughly as that of dogs. In one prospective study of 388 cats in 1963, 15 (4%) had grade one to three (out of five) systolic heart murmurs, and 8 (2%) had triple heart sounds.[6] More recently, heart diseases were diagnosed in "nearly equal" numbers of dogs and cats at the Angell Memorial Animal Hospital.[7] The types and relative frequencies of cardiopulmonary diseases in 500 cats examined clinically at that institution in 1987 to 1989 are shown in Table 23–3.[8] Hypertrophic cardiomyopathy, either idiopathic or secondary to hyperthyroidism, was the most common cardiac disorder. The annual percentage of cats diagnosed by echocardiography with pathologic left ventricular hypertrophy at The Animal Medical Center in New York has ranged from 26 to 64 percent (Fox PR, unpublished data, 1998) (chapter 28).

Necropsy studies often report a higher frequency of feline heart disease, especially if histologic studies are performed. For example, histopathologic examination of the myocardium in 50 apparently healthy cats in Israel revealed lesions in 35 (70%).[9] The largest reported series, 4933 cats necropsied at The Animal Medical Center between 1962 and 1976, disclosed acquired cardiac lesions in 421 (8.5%) cats and congenital anomalies in 96 (1.9%).[10]

TABLE 23–2
Arrhythmias Recorded in 125 of 300 Dogs with Heart Disease*

Arrhythmia Type	Number of Times Recorded
Ventricular premature beats	54
Atrial fibrillation	28
Atrial premature beats	24
Paroxysmal ventricular tachycardia	12
Supraventricular tachycardia	10
Sick sinus syndrome	5
2° AV block	5
3° AV block	4
Right bundle branch block	3
Left bundle branch block	2
Silent atrium	1
Atrial flutter	1
TOTAL	149

*All dogs with reliable signs of heart disease and owner's last name beginning with A–F in The Veterinary Hospital, University of Pennsylvania, Cardiology Section files from 1990 to 1993.

CONGENITAL HEART DISEASE

CANINE

The reported prevalence of canine congenital heart disease (CHD) from several veterinary schools was 0.46 to 0.85 percent.[1] The types and relative frequency of congenital cardiac anomalies in 1000 dogs with CHD are listed in Table 23–4. In a recent survey of 4325 dogs, CHD was detected in 0.5 percent (Fox PR, Pipers F, unpublished data). Additional data are presented in chapter 24.

The prevalence of CHD is undoubtedly greater than published percentages because some anomalies do not cause murmurs, and some severe cases result in perinatal death without necropsies. In a recent survey of 1679 purebred pet store puppies, cardiac murmurs were detected in 11 (0.65%).[11] In another report, congenital cardiovascular anomalies were found in 5 of 25 stillborn and neonatal puppies in a closed colony of

TABLE 23–4
Comparative Frequencies of Congenital Heart Defects in 1000 Dogs*

Defect	% of Dogs
Patent ductus arteriosus	27.7
Aortic stenosis	25.5
Pulmonic stenosis	20.8
Ventricular septal defect	9.8
Tricuspid dysplasia	5.1
Tetralogy of Fallot	3.9
Persistent right aortic arch	3.1
Mitral dysplasia	1.7
Atrial septal defect	1.3
Peritoneopericardial diaphragmatic hernia	0.5
Other defects	0.6
TOTAL	100.0

*1044 abnormalities in 1000 dogs at seven veterinary schools, 1986 to 1990.

beagle dogs.[12] Thus, it is probable that the true incidence of CHD is at least 1 percent of all dogs born.

The frequency of CHD in purebred dogs is greater than in mongrel dogs. This supports the view that genetic factors are important in the etiology of CHD.[13] A single gene defect was recently determined to be the cause of conotruncal abnormalities in keeshond dogs.[14]

The prevalence of congenital abnormalities differs between breeds and countries and often within regions of a given country. This indicates the importance of regional gene pools in the etiology of CHD. Thus, the reader should keep an open mind when interpreting data that may reflect the "prevalence" of certain diseases.

In a recent tabulation of the distribution of CHD in 1320 dogs in the national Veterinary Medical Data Base, there was concern about the accuracy of some diagnoses.[1] In many instances, diagnoses were entered by medical record clerks for patients that were not examined by cardiologists. Also, the breed-specific prevalence rates were based upon the breed distribution of dogs of all ages. This fails to account for shifts in breed popularities in young versus old dogs that have been noted in previous studies.[15]

Comparative Frequencies of Canine Congenital Heart Diseases

To assess current trends in breed and disease incidence, a recent study examined the types and relative frequency of diagnoses in 1000 dogs (1986 to 1990) with congenital heart disease as recorded by veterinary cardiologists* (see Table 23–4). Reference breed population data for the same period were obtained from the individual institutions or the Veterinary Medical Data Base at Purdue University; breed-specific odds ratios for each abnormality were calculated from the breed distribution of all dogs less than 3 years old presented to the seven participating institutions. The reference population age was limited to dogs under 3 years old, which represented 90 percent of the 1000 dogs. Results are summarized in Table 23–5, and data for individual abnormalities and affected breeds (Tables 23–6 to 23–10) are discussed next.

**Pennsylvania:* J. Buchanan, D. Knight; *Michigan State:* G. Eyster, C. Gabor, B. Olivier, L. Anderson, M. Probst; *Cornell:* S. Moise; *Tennessee:* R. Gompf; *Iowa:* W. Ware; *Tufts:* J. Rush; *North Carolina:* B. Keene, C. Atkins.

PATENT DUCTUS ARTERIOSUS

Patent ductus arteriosus (PDA) was the most common congenital anomaly (Table 23–4). Fifty-five differ-

TABLE 23–5
Breed Predilections in 1000 Dogs with Congenital Heart Disease*

Breed	Lesion	Relative Risk
Akita	Ventricular septal defect (VSD)	2
Basset hound	VSD	3
Bichon frise	Patent ductus arteriosus (PDA)	3
Bloodhound	Aortic stenosis (AS)	3
Boxer	Atrial septal defect (ASD)	3
	AS	3
Chihuahua	PS	2
Cocker spaniel	PDA	1
English bulldog	PS	3
	VSD	3
English springer spaniel	PDA	2
	VSD	3
German shepherd	AS	2
	Tricuspid dysplasia (TD)	2
	Persistent R aortic arch (PRAA)	2
Golden retriever	AS	3
Great Pyrenees	TD	3
Keeshond	PDA	3
Labrador retriever	TD	3
Lakeland terrier	VSD	3
Maltese	PDA	3
Miniature schnauzer	PS	2
	PDA	1
Newfoundland	AS	3
Pomeranian	PDA	2
Poodles—toy & miniature	PDA	3
Rottweiler	AS	3
Samoyed	PS	1
Scottish terrier	PS	3
Shetland sheepdog	PDA	2
Shih tzu	VSD	2
West Highland white terrier	VSD	3
	Tetralogy of Fallot	3
	PS	2
Wirehaired fox terrier	PS	3
Yorkshire terrier	PDA	2

*1044 abnormalities in 1000 dogs with CHD at seven veterinary schools from 1986 to 1990. The reference population was 32,697 dogs less than 3 years old from the same schools.

Numbers 1, 2, and 3 identify predisposed breeds repesented by three or more affected dogs in which relative risk for the indicated abnormality was significantly elevated in this series ($P < .05$ to $P < .0001$).

1, mild increased risk (odds ratio 1.5–2.9 times other dogs).
2, moderate risk (odds ratio 3–4.9 times others).
3, marked risk (odds ratio > 5 times others).

TABLE 23–6
Patent Ductus Arteriosus—Estimated Relative Risks (Odds Ratios) by Breed (n = 289)*

Breeds ≥4 Cases	No.	Odds Ratio	95% Confidence Limits	P
Maltese	12	12.4	6.4–23.4	<.0001
Toy poodle	22	6.7	4.2–10.7	<.0001
Miniature poodle	16	5.9	3.4–10.1	<.0001
Keeshond	5	5.9	2.1–15.2	.002
Bichon frise	6	5.5	2.2–13.1	.001
Pomeranian	9	4.6	2.2–9.4	<.001
Yorkshire terrier	14	4.2	2.3–7.4	<.0001
English springer spaniel	19	4.0	2.4–6.6	<.0001
Shetland sheepdog	17	3.9	2.3–6.5	<.0001
Cocker spaniel	25	2.6	1.7–4.0	<.0001
Chihuahua	4	2.8	0.9–7.8	.062
Dachshund	5	2.5	0.9–6.3	.057
Miniature schnauzer	7	2.2	0.9–4.8	.050
Australian sheepdog	4	2.0	0.6–5.6	ns
German shepherd	23	1.2	0.6–1.8	ns
Collie	5	.6	0.2–1.6	ns
Mixed breed	38	.5	0.4–0.7	.0001
Golden retriever	7	.2	0.1–0.6	.001
Labrador retriever	5	.2	0.1–0.5	.0002

*Seven veterinary schools, 1000 dogs, 1986 to 1990.
ns, not sigificant.

ent breeds represented 289 (27.7%) affected dogs from the 1000 surveyed. Breed predisposition was greatest in Maltese dogs, with an estimated risk:odds ratio of 12.4 (Table 23–6). Toy and miniature poodles still show predisposition for the disorder as was noted 30 years ago, but other breeds are also now commonly affected. Although a substantial number of German shepherds and collies had PDA, their odds ratios were not greater than would be expected by chance because of the large number of those breeds in the reference populations. Females outnumbered males by 3:1.

Cavalier King Charles spaniels have increased risk for PDA; two cases were diagnosed in the 1000-dog series yielding an odds ratio (OR) of 5.9 (95% confidence limits [CL], 1.7 to 25.1; P = .049). In Edinburgh, Scotland, 6 of 32 dogs with PDA (19%) were cavaliers, whereas the breed makes up only 1.9 percent of the clinic population (Darke PGG, personal communication).

Right-to-left shunting PDA (16 dogs) was recognized most frequently in this population of 1000 dogs in cocker spaniels (5, all females). Other breeds with more than one right-to-left shunting PDA were English springer spaniels (two) and Shetland sheepdogs (two), with one male and one female each. A recent report of hereditary PDA in 13 of 62 Pembroke Welsh corgis sired by a male with a small PDA included two with right-to-left PDA.[16] PDA also was diagnosed in six of seven corgis with congenital heart disease, as well as in five related border collies in Australia.[17, 18]

AORTIC STENOSIS

Aortic stenosis is the most common congenital heart disorder observed at the Veterinary Teaching Hospital, University of Pennsylvania,[1] but it was second in frequency in the series of 1000 dogs (see Table 23–4; these data include all forms of left ventricular outflow tract obstruction). In confirmed cases, nearly all dogs with left ventricular outflow tract obstruction have fibrous or fibromuscular subaortic stenosis (chapter 24). Newfoundland dogs are still at highest risk, but larger numbers of affected golden retrievers, rottweilers, and German shepherd dogs are detected at veterinary clinics in the United States (Table 23–7). Aortic stenosis was diagnosed in 29 of 31 Newfoundlands and 37 of 39 rottweilers with CHD. There was no sex predilection except in boxers, in which 19 of 23 dogs (83%) with aortic stenosis were males. In Scotland, boxers represent about half of the cases of subaortic stenosis.[19]

PULMONIC STENOSIS

Pulmonic stenosis (PS) is the third most frequent cause of canine congenital heart disease (see Table

TABLE 23–7
Aortic Stenosis—Estimated Relative Risks (Odds Ratios) by Breed (n = 266)*

Breeds ≥ 4 Cases	No.	Odds Ratio	95% Confidence Limits	P
Newfoundland	29	19.9	13.4–30.4	< .0001
Bloodhound	4	14.5	4.4–43.3	< .001
Boxer	23	9.3	5.8–14.7	< .0001
Golden retriever	79	6.8	5.2–9.0	< .0001
Rottweiler	37	5.4	3.7–7.8	< .0001
German shepherd	43	2.6	1.9–3.7	< .0001
Mixed breed	11	0.1	0.4–0.7	< .0001

*Seven veterinary schools, 1000 dogs, 1986 to 1990.

23–4; this includes all forms of right ventricular outflow tract obstruction in this series of 1000 dogs). In confirmed cases, dysplasia of the pulmonary valve is the most frequently observed defect in dogs, although obstruction to right ventricular outflow can develop in the infundibulum and subvalvular region, and above the pulmonic valve (chapter 24).

The estimated risk of PS was greatest in English bulldogs, but several other breeds also had elevated odds ratios (Table 23–8). There was no sex predilection except in English bulldogs, of which 18 of 25 dogs (72%) were male. The importance of coronary artery anomalies with pulmonic stenosis has been highlighted in several reports.[20–22] The majority of English bulldogs with PS recently evaluated at my institution have had an anomalous single coronary artery with an aberrant left main coronary artery arising from a large single right coronary artery, and encircling and constricting the base of the pulmonic valve.[20] Coronary angiography always should be performed in this breed as an adjunct to planning surgery.

Valvular PS was reported in four male Boykin spaniels in Georgia,[23] and other cases have been seen in Virginia and Alabama.[1] Thickened, dysplastic valves are the cause of the stenosis. The Boykin spaniel is a common hunting dog breed in the Southeast but is not reflected significantly in national data. Southeastern institutions did not contribute data for the 1000-dog study reported in this chapter. A similar form of PS in beagles was shown to be hereditary,[24] but only two beagles had PS in the 1000-dog study, and the breed did not have elevated risk. Auscultation of 3586 young and adult beagles revealed 16 dogs with pulmonic stenosis (Moise NS, personal communication).

Mastiffs had increased risk for PS in the United States during an early survey, with an odds ratio of 11.6.[1] However, they are not a common breed in this area, and only one mastiff and two bullmastiffs with PS were detected in the 1000-dog series. Recently, six bullmastiffs with PS were confirmed over a 3-year period in Australia,[25] and 2 of 42 dogs with PS in the United Kingdom were bullmastiffs.* Thus, mastiff breeds have an increased risk for PS.

TABLE 23–8
Pulmonic Stenosis—Estimated Relative Risks (Odds Ratios) by Breed (n = 217)*

Breeds ≥ 4 Cases	No.	Odds Ratio	95% Confidence Limits	P
English bulldog	24	12.9	8.1–20.2	< .0001
Scottish terrier	7	12.6	5.3–28.5	< .0001
Wirehaired fox terrier	5	10.5	3.7–27.3	< .001
Miniature schnauzer	11	4.7	2.4–9.0	< .0001
West Highland white terrier	5	4.2	1.5–10.8	.008
Chihuahua	4	3.7	1.2–10.4	.026
Samoyed	6	2.7	1.1–6.4	.027
Yorkshire terrier	5	1.9	0.7–4.8	ns
Cocker spaniel	12	1.6	0.8–2.9	ns
German shepherd	15	1.1	0.6–1.8	ns
Collie	6	1.1	0.4–2.5	ns
Golden retriever	7	0.5	0.2–1.1	ns
Labrador retriever	7	0.4	0.2–0.8	.02
Mixed breed	18	0.3	0.2–0.5	< .0001

*Seven veterinary schools, 1000 dogs, 1986 to 1990.
ns, not significant.

TABLE 23–9
Ventricular Septal Defect—Estimated Relative Risks (Odds Ratios) by Breed (n = 102)*

Breeds ≥ 3 Cases	No.	Odds Ratio	95% Confidence Limits	P
Lakeland terrier	3	998.7	97.0–1635	< .0001
West Highland white terrier	7	13.4	5.6–30.4	< .0001
English springer spaniel	9	5.4	2.6–11.2	< .0001
Basset hound	4	5.3	1.6–15.0	.008
English bulldog	5	5.0	1.8–12.9	.004
Akita	3	4.1	1.4–13.4	.041
Shih tzu	4	3.3	1.0–9.3	.038
Miniature poodle	3	2.9	1.0–9.7	ns
Husky	4	2.5	0.8–7.0	ns
Chow	3	2.4	0.8–7.8	ns
Beagle	3	2.4	0.8–7.7	ns
Labrador retriever	4	0.5	0.2–1.4	ns
Mixed breed	11	0.4	0.2–0.8	.005

*Seven veterinary schools, 1000 dogs, 1986 to 1990.
ns, not significant.

VENTRICULAR SEPTAL DEFECT

Ventricular septal defect (VSD) has been recognized in various breeds. English springer spaniels were most often seen in the 1000-dog series. Odds ratios were greater in West Highland white terriers and Lakeland terriers (Table 23–9). Three of four Lakelands with congenital heart disease had VSD. No sex predilection was observed. A report documenting the occurrence of ventricular septal defects in a group of closely related English springer spaniels indicated that the defect was heritable.[25a] The exact mode of inheritance was uncertain, but no sex predilection was identified.

TRICUSPID VALVE DYSPLASIA

Tricuspid dysplasia has increased in frequency in recent years, particularly in Labrador retrievers (see Table 23–5).[1] A series of 14 dogs with the abnormality 20 years ago did not include any Labradors.[26] This lesion usually occurs as an isolated abnormality, but it sometimes accompanies pulmonic stenosis or mitral dysplasia. As an isolated abnormality, it is most common now in Labrador retrievers (22 dogs: OR, 8.41;

*United Kingdom survey of congenital heart disease in 339 dogs: 1989 to 1993. Contributors: D. Clarke, M. Cobb, P.G.G. Darke, J.D. McEwan, M. Herrtage, S. Johnstone, C. Little, V. Luis-Fuentes, M. Oakley. Veterinary Cardiovascular Society Newsletter, 1994.

CL, 4.7 to 15.0; P < .0001) and German shepherds (10 dogs: OR, 3.1; CL, 1.5 to 6.5; P = .003). Four Great Pyrenees also were observed (OR, 43.6; CL, 12.9 to 131.0; P < .0001). There was a male predominance, with males accounting for all 10 German shepherds, 3 of 4 Great Pyrenees, and 14 of 22 Labrador retrievers. Overall, males represented 71 percent of 53 dogs with tricuspid dysplasia. Three dogs with Ebstein's anomaly (one Labrador retriever, one Old English sheepdog, and one Irish wolfhound) were included under tricuspid dysplasia.

MITRAL VALVE DYSPLASIA

Mitral dysplasia (malformation) with regurgitation was reported in 18 of 1000 dogs with congenital heart disease, including 3 German shepherds (OR, 2.7; CL, 0.8 to 9.8; P = .125, all males). Other breeds represented by two animals each were golden retriever and the Dalmatian. Previous reports suggested a predisposition for congenital mitral insufficiency in Great Danes and German shepherds.[27, 28] However, reference population data were not given, preventing odds ratios from being determined.

Recent studies indicate that bull terriers also are predisposed to congenital mitral valve disease. Significant breed abnormalities were not found in the 1000-dog series (see Table 23–5). However, the three dogs (8 to 10 years old) with mitral stenosis at the Veterinary Hospital, University of Pennsylvania, prior to 1985 were bull terriers. At Ohio, 4 of 15 young dogs with mitral stenosis were bull terriers, and 5 were Newfoundlands.[29] Most of them also had mitral insufficiency, and 8 of 15 had subaortic stenosis. Two other reported cases of mitral stenosis were bull terriers.[30] In Australia, 11 young bull terriers with mitral insufficiency were identified over a period of 10 years, but no mention was made of coexistent mitral stenosis.[31] In the United Kingdom, 29 of 49 dogs with mitral dysplasia were bull terriers* (the large number of cases stemmed from specific screening of the breed for evidence of mitral dysplasia).

TETRALOGY OF FALLOT

Tetralogy of Fallot (TF) occurs in a variety of breeds, particularly those which also have increased risk for either PS or VSD. In the series of 1000 dogs, any dog with both PS and VSD was categorized as tetralogy of Fallot. Breed associations for the three lesions (PS, VSD, TF) are consistent with genetic studies in keeshond dogs which showed that all three defects can be variations of conotruncal abnormalities associated with a single gene defect in that breed.[14] The 1000-dog series included 41 cases of tetralogy of Fallot with wirehaired fox terriers (two dogs: OR, 22.0; CL, 8.1 to 95.4; P = .004) and West Highland white terriers (three dogs: OR, 14.1; CL, 5.7 to 48.0; P = .002) having greatest risk. Only one keeshond was identified.

PERSISTENT RIGHT AORTIC ARCH

Persistent right aortic arch (PRAA) and related vascular rings cause impaired swallowing in dogs. Many cases are diagnosed by radiologists and are treated surgically without examination by cardiologists, unless a coexistent abnormality is detected. For this reason, the 32 dogs with PRAA in 1000 dogs seen by cardiologists (see Table 23–4) do not reflect the number of cases actually presented and treated at various institutions during the comparable time period. Three breeds with increased risk were German shepherd (eight dogs: OR, 4.5; CL, 1.9 to 10.5; P = .001), Brittany spaniel (two dogs: OR, 9.3; CL, 2.9 to 40.1; P = .022), and bulldog (two dogs: OR, 6.5; CL, 1.9 to 27.8; P = .043). No Irish setters were reported.

ATRIAL SEPTAL DEFECTS

Atrial septal defects are uncommon in dogs. Three of the 14 cases represented from the 1000 dogs were boxers (OR, 25; CL, 10.8 to 98.1; P < .001), and two were Newfoundlands (OR, 24; CL, 8.6 to 113; P < .005). Other reports of a predilection for atrial septal defect in the Doberman pinscher and Samoyed breeds were not confirmed in the 1000-dog study (Table 23–10).

FELINE

Whether congenital heart disease is more or less prevalent in cats compared with dogs is uncertain, although different anomalies predominate in cats. The frequency of congenital heart disease in cats was 0.2 per 1000 feline admissions and 28 per 1000 necropsies at the Angell Memorial Animal Hospital during the period from 1957 to 1979.[32] In dogs, similar clinical and necropsy frequencies were observed at that institution. In contrast, the clinical frequency of CHD in dogs at the Veterinary Hospital, University of Pennsylvania, was much higher (5 per 1000 admissions or 10/1000 if referred cases were included) in the specific cardiovascular epidemiologic study from 1958 to 1961.[3]

Combined data from 287 cats with CHD indicate that mitral and tricuspid valve malformations were the most common abnormality (17%), followed by VSD (15%), endocardial fibroelastosis (11%), PDA (11%), vascular anomalies (8%), aortic stenosis (6%), tetral-

*United Kingdom survey of congenital heart disease in 339 dogs: 1989 to 1993. Contributors: D. Clarke, M. Cobb, P.G.G. Darke, J.D. McEwan, M. Herrtage, S. Johnstone, C. Little, V. Luis-Fuentes, M. Oakley. Veterinary Cardiovascular Society Newsletter, 1994.

TABLE 23–10
Additional Breed Predilections for Congenital Heart Disease (Confirmed or Suggested by Others)

Breed	Suggested Predilection
Airdale terrier	Pulmonic stenosis (PS)
Beagle	PS
Boykin spaniel	PS
Bullmastiff	PS
Bull terrier	Mitral dysplasia (MD)
Chihuahua	Patent ductus arteriosus (PDA)
Cocker spaniel	PS
Collie	PDA
Doberman pinscher	Atrial septal defect (ASD)
English bulldog	Tetralogy of Fallot (TF) Aortic stenosis (AS)
German shepherd	MD, PDA
German shorthair pointer	AS
Golden retriever	Tricuspid dysplasia (TD)
Great Dane	AS, PRAA, MD, TD
Irish setter	Persistent right aortic arch
Keeshond	TF
Kerry blue terrier	PDA
Mastiff	PS
Samoyed	AS, ASD
Weimaraner	TD, peritoneopericardial hernia

Adapted from Buchanan JW. Causes and prevalence of cardiovascular disease. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 647.

ogy of Fallot (6%), atrial septal defect (4%), common atrioventricular canal (4%), and pulmonic stenosis (3%). Male predominance was reported for AV valve malformation (5:1), aortic stenosis (3:1), endocardial fibroelastosis (9:5), and tricuspid dysplasia (6:1).[32]

ACQUIRED HEART DISEASE

CHRONIC VALVULAR DISEASE (ENDOCARDIOSIS)

Chronic valvular disease is the most common canine acquired disorder (see Table 23–1) and results from myxomatous valvular degeneration (chapter 25). Mitral regurgitation occurs in more than one third of dogs over 10 years of age.[15] In a recent survey of 4325 dogs at the Animal Medical Center in New York City, 9 percent were affected (Fox PR, Pipers FS, unpublished data). It is more prevalent in small breeds, with a slightly (but significantly) greater frequency and severity in males. Breed predisposition includes the toy and miniature poodle, miniature schnauzer, Pomeranian, Chihuahua, cocker spaniel, Pekingese, fox terrier, and Boston terrier breeds in the United States,[15] and in male miniature pinschers, whippets and cavalier King Charles spaniels in Great Britain.[33] In a recent survey at the Veterinary Hospital, University of Pennsylvania, small canine breeds still predominated, and no large-breed dogs had an increased risk (Table 23–11). The exceptionally high occurrence of this disease in cavalier King Charles spaniels was confirmed in screening clinics in Great Britain,[34] Sweden,[35] and the United States,[36] but investigators in Australia did not find evidence of an increased prevalence in the breed.[37] Auscultation of 394 cavaliers in the United States revealed systolic murmurs of mitral regurgitation in 56 percent of dogs over 4 years of age, and in 100 percent of those 10 years old or older.[36]

Limited necropsy studies indicate that chordal lengthening or rupture with or without significant valve thickening are common features. Mitral prolapse and left atrial rupture also have been found. Left atrial rupture as a complication of chronic acquired valvular disease also occurs in miniature poodles, cocker spaniels, and dachshunds, with predominance in males.[38]

Clinically significant acquired mitral valve disease is uncommon in cats (Fox PR, personal communication). One review of necropsies reported mitral valve disease in 11 of 202 cats (5%), whereas a frequency of 40 percent was observed in 500 dogs in the same laboratory.[39] "Mitral insufficiency of unknown cause" was reported in 75 (15%) of 500 cats,[8] although no details were provided as to whether diagnosis was confirmed by Doppler echocardiography or just based upon auscultation. Flow murmurs and aortic outflow turbulence occur in cats and can be misdiagnosed as mitral regurgitation.

HEMATOCYSTS

Blood cysts (hematocysts) in atrioventricular valves, particularly the tricuspid valve, are occasional necropsy findings in young dogs but rarely have any clinical

TABLE 23–11
Chronic Valvular Disease (n = 120): Estimated Relative Risks (Odds Ratios) by Breed*

Breeds ≥ 3 Cases	No.	Odds Ratio	95% Confidence Limits	P
Cavalier King Charles spaniel	4	20.1	5.5–67	.0001
Chihuahua	6	5.5	2.1–13.3	.001
Miniature schnauzer	7	4.4	1.8–10.1	.002
Maltese	3	4.2	1.4–14.1	.041
Pekingese	3	4.1	1.4–13.8	.043
Toy poodle	5	3.1	1.1–8.1	.028
Shih tzu	5	3.0	1.1–7.8	.031
Miniature poodle	8	2.8	1.2–6.0	.012
Yorkshire terrier	5	2.6	0.9–6.8	.051
Lhasa apso	4	2.4	0.7–6.8	ns
Cocker spaniel	7	2.0	0.9–4.6	ns
Mixed breed	36	1.2	0.8–1.7	ns
Doberman pinscher	3	0.8	0.3–2.6	ns

*120 dogs with chronic valvular disease out of 300 dogs with reliable signs of heart disease and owner's last name A-F in The Veterinary Hospital, University of Pennsylvania, Cardiology Section files from 1990 to 1993.
ns, not significant.

significance.[40] A survey of 255 beagle dogs 5 to 24 months old detected blood cysts in the septal leaflet of the tricuspid valve in 11 cases (3.9%).[41] Serial section histology and immunohistochemistry showed that the blood cysts came from vessels in the valves and did not communicate directly with the cardiac chambers. In late stages, the cysts often were surrounded by fibrous tissue, and metaplastic bone was sometimes present within the lesions.

BACTERIAL ENDOCARDITIS

Bacterial endocarditis is uncommon (chapter 26). It was diagnosed in 3 of 300 dogs (1%) with reliable signs of heart disease in our clinic (see Table 23–1); 10 of 345 dogs (3.0%) at another institution had echocardiographic signs of endocarditis.[42] A recent review of the Veterinary Medical Data Base from January 1984 through May 1994 indicated that endocarditis was diagnosed in 0.04 to 0.13 percent of dogs and in 0.006 to 0.024 percent of cats presented for veterinary services.[42a] This same report also indicated that the prevalence of endocarditis in dogs increases with age. In the absence of an echogenic thrombus or aortic regurgitation, a clinical diagnosis of endocarditis is difficult to confirm, and most epidemiologic data are based on necropsy studies.

The overall reported necropsy prevalence varies from 0.06 to 6 percent and depends upon the diligence and interest of the investigator. The mitral and aortic valves are most often affected, and the most common organisms isolated are *Staphylococcus aureus*, streptococci, and *Escherichia coli*.[43] Endocarditis is often associated with infection elsewhere in the body. Prostate infections were the most frequent coexisting infection in 40 dogs with endocarditis in one study.[44] Infective and noninfective arthritis were found in 12 dogs with endocarditis in another series.[45] All ten dogs in a recent report were large breeds.[46] Five strains of *Erysipelothrix tonsillarum* were isolated from dogs with endocarditis in Belgium.[47]

MYOCARDIAL DISEASES (CARDIOMYOPATHIES)

Cardiomyopathy denotes structural or functional derangement of the heart muscle (myocardial disease) that is not attributable to valvular, vascular, or congenital disorders. A wide variety of primary and secondary causes have been described (chapters 27, 28).

There is increased recognition of myocardial disease over the last 2 decades. This is due to improved diagnostic capability associated with echocardiography, as well as an increased frequency of cardiomyopathy in certain breeds such as Doberman pinscher and boxer dogs.

The prevalence of myocardial disease varies with geographic factors (e.g., Chagas' disease in southern border states), the nature of the study (clinical or pathologic), and type of diagnostic criteria selected. Necropsy studies consistently reveal a higher prevalence of myocardial disease than do clinical investigations. The types and pathology of most myocardial diseases in all species of animals have been thoroughly reviewed by Van Vleet and Ferrans.[48]

CANINE CARDIOMYOPATHIES

From 1958 to 1960, the prevalence of myocardial disease (based mainly on the detection of arrhythmias) in 5000 dogs was 0.45 percent. In a 1988 study of 7148 dogs, dilated cardiomyopathy (DCM) was diagnosed in 1.1 percent.[4] A tabulation of 300 dogs with arrhythmia or echocardiographic left ventricular shortening fractions of less than 25 percent disclosed that 45 percent had probable myocardial disease (see Tables 23–1 and 23–2). A review of the Purdue Veterinary Medical Data Base (January 1986 through December 1991) indicated that DCM was diagnosed in approximately 0.5 percent of the dogs presented for veterinary services (1681 of 342,152 dogs)[49]; DCM was detected in 0.5 percent of 4325 dogs recently surveyed in New York City (Fox PR, Pipers F, unpublished data).

Large breeds of dogs, especially males, are predisposed to dilated (congestive) cardiomyopathy. A particular susceptibility has been recognized in Doberman pinscher dogs. Of 68 dogs with DCM reported from the University of Georgia in 1986, 39 (57%) were Dobermans.[50] In the recent sample of 300 dogs with reliable signs of heart disease in our clinic (Table 23–1), DCM was diagnosed in 34 dogs, of which 17 (50%) were Dobermans (OR, 33.7; CL, 16.2 to 70.4; $P < .0001$). Males predominated in Dobermans as well as in the other breeds represented (82%).

According to a review of the Veterinary Medical Data Base (January 1986 through December 1991),[49] the prevalence rate of DCM in mixed-breed dogs was approximately 0.16 percent compared with 0.65 percent in purebred dogs. The prevalence rate of DCM was highest in Doberman pinschers (5.8%), Irish wolfhounds (5.6%), Great Danes (3.9%), boxer dogs (3.4%), Saint Bernards (2.6%), Afghan hounds (1.7%), Newfoundlands (1.3%), and Old English sheepdogs (0.9%). By comparison, the prevalence of DCM was 0.69 percent in English cocker spaniels and 0.34 percent in American cocker spaniels. The prevalence of DCM increased with age, and males were affected nearly twice as often as females.

Other breed-associated cardiomyopathies include arrhythmogenic cardiomyopathy in boxer dogs,[51] DCM in Old English sheepdogs[52] and Newfoundland dogs

in Sweden,[53] familial cardiomyopathy in English cocker spaniels,[54] and Duchenne's X-linked muscular dystrophy cardiomyopathy in male golden retriever dogs.[55] Hypertrophic cardiomyopathy is quite rare in dogs, but a hereditary form has been reported in pointer dogs.[56, 57]

Cardiomyopathy may result from other factors. This has been shown to result from certain types of chemotherapy, particularly doxorubicin administration. Five to 15 percent of dogs treated with this drug developed congestive heart failure, and cardiotoxicosis is the major dose-limiting factor for extended chemotherapy for neoplasia.[58, 59]

MYOCARDITIS. The frequency of parvovirus myocarditis has diminished greatly since the advent of vaccination programs, and no cases have been recognized in our clinic in recent years. A retrospective histopathologic study utilizing *in situ* hybridization technology revealed evidence of parvovirus-specific nucleic acid in the myocardium of some puppies without intranuclear inclusion bodies, but there was no evidence of infection after 1979 in Zurich, Switzerland.[60]

Occasional dogs with arrhythmias are seropositive for *Borrelia burgdorferi.* However, the significance of titers in our region is uncertain, and it is difficult to substantiate a clinical diagnosis of Lyme disease myocarditis.[61, 62] Chagas' myocarditis due to *Trypanosoma cruzi* still appears to be limited to occasional dogs in southern border states.[63]

FELINE CARDIOMYOPATHIES

Diagnosis of feline cardiomyopathies has been greatly facilitated by echocardiography. Hypertrophic cardiomyopathy (HCM) is currently the most frequent type of feline myocardial disease. It may be primary[64] or secondary.[65] Based upon echocardiography logs, pathologic left ventricular hypertrophy was recorded in 26 to 64 percent of cats evaluated at the Animal Medical Center from 1985 to 1998 (chapter 28; Fox PR, personal communication).

In a retrospective review of 1472 feline necropsies from 1986 to 1992 at the Veterinary Hospital, University of Pennsylvania, dilated cardiomyopathy was diagnosed in 33 cats (2.2%); hypertrophic cardiomyopathy in 34 (2.3%); restrictive cardiomyopathy in 25 (1.7%); and endomyocarditis in 37 (2.5%).[66] All cases of dilated cardiomyopathy occurred prior to 1991, and hypertrophic cardiomyopathy is now the most frequently recognized form at necropsy.

Some types of restrictive cardiomyopathy may represent a late stage of endomyocarditis.[66, 67] Endomyocarditis occurred primarily in young cats (mean age, 3.4 years); frequently followed a stressful event such as neutering, declawing, or vaccination; and was often accompanied by interstitial pneumonia.[67] The term "intermediate" cardiomyopathy used by some investigators lacks definition, and associated reports are difficult to evaluate.

The prevalence of feline dilated cardiomyopathy (DCM) has declined profoundly since taurine deficiency was recognized as a major etiologic factor and following commercial diets supplemented with taurine.[68] Occasional cats with DCM have normal taurine levels, and it is apparent that other etiologies remain to be identified.[69–72] Differences in the frequency of DCM in separate colonies of inbred cats suggest that quantitative genetic factors may influence susceptibility to the disease.[71]

ENDOMYOCARDITIS AND ENDOMYOCARDIAL FIBROSIS. These entities occur more commonly in cats than in dogs. In cats, they may result in restrictive cardiomyopathy when the subendocardial myocardium is significantly involved or if large endocardial scar formation develops. Additional information is presented later under feline cardiomyopathy (chapter 28).

EXCESSIVE LEFT VENTRICULAR MODERATOR BANDS (FALSE TENDONS). In cats, excessive numbers and configurations of left ventricular moderator bands (false tendons) have been reported in association with feline myocardial diseases.[73] Their significance remains uncertain and they are a frequent necropsy finding.

ENDOCARDIAL FIBROELASTOSIS

Endocardial thickening with mild fibrosis and increased elastic fibers may occur in response to chronic dilatation and diastolic pressure overload. The degree of secondary thickening in this circumstance is not clinically significant, and signs are related to the underlying valvular or myocardial disorder. More severe primary endocardial fibroelastosis with clinical signs indistinguishable from those of dilated cardiomyopathy was reported in four young dogs of different breeds.[74] Although the etiology was unknown, the age suggests a congenital abnormality. In a hereditary form of fibroelastosis in Burmese cats, the endocardium progressed from normal histology at birth to symptomatic fibroelastosis by 2 months of age.[75]

BREED-ASSOCIATED ARRHYTHMIAS

A variety of ventricular or atrial arrhythmias may occur in most forms of advanced heart disease. In addition, some breeds are known to develop specific arrhythmias more than others.

SICK SINUS SYNDROME. The most characteristic example is syncope due to sick sinus syndrome, which most commonly occurs in female miniature schnauzers.[76] A recent analysis of 318 affected dogs showed an odds ratio of 6.9 in miniature schnauzers. At the Veterinary Hospital, University of Pennsylvania, 10 of 15 dogs were miniature schnauzers (OR, 126). Additional breed predispositions were also noted in Pomeranians (OR, 3.5), boxers (OR, 2.6) and cocker spaniels (OR, 1.7).[1] Sex differences were significant only in miniature schnauzers, in which the female-to-male ratio was 3:1.

VENTRICULAR ECTOPY. Ventricular extrasystoles with paroxysmal ventricular tachycardia, flutter, and fibrillation were recognized as a familial arrhythmia causing sudden death in a family of German shepherds in New York.[77] Further studies identified four families of affected German shepherd dogs, all of which were related to a common ancestor.[78] Additional cases have been identified in other states and in Great Britain, indicating widespread distribution of the genetic predisposition for sudden arrhythmic death in this breed (Moise NS, personal communication). Ventricular ectopy is also the predominant arrhythmia seen in boxer cardiomyopathy.[51]

OTHER BREED-ASSOCIATED ARRHYTHMIAS. These include AV conduction block in pugs with hereditary stenosis of the bundle of His,[79] and sudden death in Doberman pinschers.[80] Persistent atrial standstill characterized by absence of atrial muscle and associated P waves in young dogs is rare but occurs predominantly in English springer spaniels. This breed represented 20 of 29 dogs with atrial standstill in combined totals from five reports.[1, 81–84] It was associated with varying degrees of scapulohumeral muscle wasting in 30 percent of the dogs in one report. Eight of 11 cats with atrial standstill were Siamese.[83]

ATRIAL FIBRILLATION. Atrial fibrillation is usually associated with significant heart disease in dogs and cats and is not a breed-specific arrhythmia. However, it is occasionally noted in large-breed, asymptomatic dogs. A particularly high frequency was observed in Irish wolfhounds during screening surveys of 496 wolfhounds and 92 English mastiffs for evidence of cardiomyopathy.[85] Only four of the wolfhounds were symptomatic for heart disease, but 52 (10.5%) had atrial fibrillation; 22 had ventricular premature beats and some had other arrhythmias. None of the mastiffs had atrial fibrillation, but a few had other arrhythmias. There was no sex difference in the frequency of atrial fibrillation in this series, but the frequency showed a positive correlation with body size in both sexes.[86] Others have reported greater frequency of atrial fibrillation in male dogs.[87–89]

PERICARDIAL DISEASE AND NEOPLASIA

Certain changes have been noted in the prevalence of primary and secondary pericardial diseases. The most common disorder, pericardial effusion, has been recently recorded almost exclusively in large breeds of nonbrachycephalic dogs of either sex.

At the Veterinary Hospital, University of Pennsylvania, pericardial effusion was diagnosed or confirmed by echocardiography in 7 percent of the dogs with reliable signs of heart disease (see Table 23–1). Although recognition of pericardial effusion has increased with the advent of echocardiography, the incidence also has increased in certain breeds, particularly golden retrievers.[1] In a series of 92 dogs with pericardial disease evaluated from 1987 to 1989, there was an increased risk of pericardial effusion in golden retrievers (n = 22, OR, 7.4), German shepherds (n = 14; OR, 2.3), and Labrador retrievers (n = 8; OR, 2.2), German shorthair pointers (n = 4; OR, 9.5), and Akitas (n = 3; OR, 6.5).[1] Brachycephalic breeds were uncommon and were represented by only three boxer dogs (OR, 1.5), one bulldog, and one Boston terrier. Golden retrievers (6) and German shepherds (4) were the most common breeds represented in 21 dogs with pericardial effusion in 1990 to 1993 (see Table 23–1) and were also recognized in reports by others.[90–92] Most pericardial effusions are caused by hemorrhage from primary or metastatic hemangiosarcomas, but occasional dogs are recognized with chemodectoma, mesothelioma, various other sarcomas and carcinomas, idiopathic benign pericardial effusion, congestive heart failure, uremia, infection, foreign body, trauma, cysts, congenital pericardioperitoneal hernia, or ruptured left atrium.

Neoplasia was identified as the cause of pericardial effusion in 24 of 42 dogs (57%) in one series[90] and 19 of 50 (38%) in another report.[93] A mass was visible in 12 of 21 dogs with pericardial effusion at this institution, and 9 other dogs were found to have cardiac tumors without effusion (see Table 23–1). Hemangiosarcoma is the most common primary cardiac neoplasm in dogs. It is usually located in the right atrium or right atrial appendage and was previously recognized most often in German shepherd dogs.[94–96] More recently, it has been seen commonly in golden retrievers at the Veterinary Hospital, University of Pennsylvania.[92] Chemodectomas are the second most common cardiac neoplasm. They occur with increased frequency in brachycephalic breeds, particularly males,[97, 98] but are also recognized in nonbrachycephalic dogs.[91, 97, 99]

Feline pericardial disease (mainly effusion) was diagnosed in 66 of 2852 feline necropsies (2.3%).[100] In most instances, the effusion was associated with other illnesses, including feline infectious peritonitis, cardiomyopathy, renal failure, systemic infection, coagulopa-

thies, or neoplasia (lymphosarcoma or metastatic carcinoma). Hemangiosarcoma and benign idiopathic pericardial effusion were not observed. In another review of 4933 feline necropsies, no primary cardiac tumors were found, but 18 cases of hemangiosarcoma were identified.[101] Cardiac metastases were identified in 12 cats, but none were in the right atrium.

PULMONARY VASCULAR DISEASE

The most common pulmonary vascular disease in dogs is pulmonary arteritis and thromboembolism due to *Dirofilaria immitis* infection (chapter 30). Although dirofilariasis is widespread in the United States, the frequency and pattern of distribution generally correspond to climatic conditions favoring maturation of larvae and survival of mosquito vectors. The disease occurs in cats much less frequently than in dogs. In endemic areas, 11 necropsy surveys showed average heartworm infection rates of 1.9 percent in cats and 34.6% in dogs.[102]

Pulmonary thromboembolism complicating other diseases was suspected clinically in only 2 of 47 dogs with emboli at necropsy.[103] The most commonly associated diseases were cardiac (15), neoplasia (14), and disseminated intravascular coagulopathy (10). Another necropsy survey of vascular thrombosis in 59 dogs excluded those conditions.[104] Pulmonary thromboemboli were found in 27 of 59 dogs, and the most commonly associated conditions were renal disease (11 of 27) and hyperadrenocorticism or steroid therapy (11 of 27). Portal vein thrombi in 11 dogs were mainly associated with steroid therapy (10 of 11) and pancreatic necrosis (4 of 11).[105]

Medial hyperplasia of pulmonary arterioles is often observed histologically in cats, but it is not usually associated with recognizable clinical disease. Reported occurrence rates vary from 3 to 68 percent because of nonspecific criteria for histologic diagnosis and variable interest on the part of the observers. One study focusing on cardiovascular pathology reported a frequency of 68.8 percent in 122 cats and found no age group differences in cats older than 1 year.[39] Identical lesions were found in specific pathogen-free cats, indicating that pulmonary artery parasitism was not a major etiologic factor.[106]

SYSTEMIC VASCULAR DISEASE

Primary systemic vascular disease is uncommon, but atherosclerosis and aortic or coronary thrombosis are occasionally recognized, particularly in dogs with hypothyroidism and elevated serum cholesterol.[107] Intramural coronary arteriosclerosis with amyloid deposition is common in old dogs with chronic valvular disease.[108] Intramural coronary arteriosclerosis without amyloid also occurs in the left ventricle of dogs with congenital subaortic stenosis and in the right ventricle of dogs with pulmonic stenosis. Spontaneous, asymptomatic coronary artery vasculitis of unknown etiology has been recognized in up to 34 percent of young beagles.[109, 110] Systemic vasculitis causing a canine pain syndrome also has been reported in young beagles from several laboratories in the United States, France, and Great Britain over the past 10 years.[111] Immunologic studies have shown that the disorder is comparable to Kawasaki disease in humans, and it has been termed canine juvenile polyarteritis syndrome.[112] Systemic arterial thrombi are uncommon in dogs. In a series of 29 dogs with arterial thrombi, 7 had primary renal disease.[104] Congenital or acquired peripheral arteriovenous fistulas occur, usually in limbs and secondary to trauma.[113]

Portacaval shunts are the second most common canine congenital cardiovascular malformation.[1] Analysis of breed distribution in 298 dogs and respective odds ratios showed the most frequent occurrence in Yorkshire terriers (OR, 19.9), pugs (10.0), miniature schnauzers (6.9), Maltese (5.4), Pekingese (3.7), standard schnauzers (3.7), Shih tzu (3.4), and Lhasa apso (2.4).[1]

Aortic thromboembolism in cats is the most frequent vascular abnormality encountered in small animal medicine and may occur with any form of cardiomyopathy. The frequency of aortic thromboembolism in 2000 cats presented to the Veterinary Hospital, University of Pennsylvania, in 1961 to 1964 was 0.7 percent.[114] Thirty years later, during 1991 to 1993 it was diagnosed in 53 of 8350 cats (0.63%), which suggests that the occurrence rate may not have changed despite a major reduction in the incidence of dilated cardiomyopathy. The predominance in males 30 years ago (2.9:1) was still present in 53 recent cases (2.5:1). However, the average age of affected cats today (8.4 years) was greater than 30 years ago (5.6 years, P = .007).

SYSTEMIC HYPERTENSION

Systemic hypertension in small animals appears to be more common than studies indicated 30 years ago. This stems from better recognition of associations between hypertension and end-organ diseases (e.g., retinal hemorrhage in cats presented for sudden blindness).[115] Diagnosis has been hampered by lack of confidence in indirect blood pressure measurement techniques and increased blood pressure that occurs with excitement in untrained dogs and cats.[116] Cyclic blood pressure variations have also been demonstrated by 24-hour recordings in a colony of dogs with hereditary hypertension.[117] One report suggests that criteria for hypertension require blood pressures greater than

180 mmHg systolic or greater than 100 mmHg diastolic.[118] Surveys in clinically normal dogs revealed elevated arterial blood pressures in 1 to 2 percent of dogs.[119] Caution should be exercised when extrapolating values from other breeds to greyhounds that may have higher normal systolic pressures (normally > 200 mmHg).[120]

Animals with end-organ disease due to hypertension commonly have systolic arterial pressures of 220 to 240 mmHg. About one third of dogs with hypertension have chronic renal disease and one third have hyperadrenocorticism. Most cats with hypertension have chronic renal disease or hyperthyroidism.[115]

REFERENCES

1. Buchanan JW. Causes and prevalence of cardiovascular disease. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 647
2. Patterson DF. Epidemiologic and genetic studies of congenital heart disease in the dog. Circ Res 23:171, 1968
3. Detweiler DK, Patterson DF. Prevalence and types of cardiovascular disease in dogs. Ann NY Acad Sci 127:481, 1965
4. Fioretti M, Delli Carri E. Epidemiological survey of dilatative cardiomyopathy in dogs. Veterinaria 2:81, 1988
5. Ferro E, Brambilla PG, Faverzani S, Traditi E. Epidemiologia delle malattie cardiovascolari del cane: Risultati dei primi quatro anni di indagini. (Epidemiology of cardiovascular diseases in dogs: Results of first four years of investigations). Veterinaria 4:5, 1990
6. Tashjian RJ, Pennsinger RR, Das KM, et al, Feline cardiovascular studies—a preliminary report. Proceedings, American Veterinary Medicine Association Annual Meeting, 1965, p 112
7. Harpster NK. Cats don't have heart disease. Proceedings, Academy of Veterinary Cardiology, 1990, p 22
8. Harpster NK. Feline arrhythmias: Diagnosis and management. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 732
9. Nobel TA, Newmann F, Klopfer U. Histopathology of the myocardium in 50 apparently healthy cats. Lab Anim 8:119, 1974
10. Liu SK. Pathology of feline heart diseases. Vet Clin North Am 7:323, 1977
11. Ruble RP, Hird DW. Congenital abnormalities in immature dogs from a pet store: 253 cases (1987–1988). J Am Vet Med Assoc 202:633, 1993
12. Zaldivar R. Incidence of spontaneous diseases in a Beagle colony. J Am Vet Med Assoc 151:1186, 1967
13. Patterson DF. Hereditary congenital heart defects in dogs. J Small Anim Pract 30:153, 1989
14. Patterson DF, Pexieder T, Schnarr WR, et al. A single major gene defect underlying cardiac conotruncal malformations interferes with myocardial growth during embryonic development: Studies in the CTD line of keeshond dogs. Am J Hum Genet 52:388, 1993
15. Buchanan JW. Chronic valvular disease (endocardiosis) in dogs. Adv Vet Sci Comp Med 21:75, 1977
16. Oswald GP, Orton EC. Patent ductus arteriosus and pulmonary hypertension in related Pembroke Welsh Corgis. J Am Vet Med Assoc 202:761, 1993
17. Hunt GB, Church DB, Malik R, Bellenger CR. A retrospective analysis of congenital cardiac anomalies (1977–1989). Aust Vet Pract 20:70, 1990
18. Malik R, Turnbull GR, Black AP. Patent ductus arteriosus in 5 related Border Collies. Aust Vet Pract 21:2, 1991
19. Fuentes VL, Dukes J. Systolic cardiac murmurs in boxers. Vet Rec 129:343, 1991
20. Buchanan JW: Pulmonic stenosis caused by single coronary artery in dogs: Four cases (1965–1984). J Am Vet Med Assoc 196:115, 1990
21. Minami T, Wakao Y, Buchanan JW, et al. A case of pulmonic stenosis with single coronary artery in a dog. Jpn J Vet Sci 51:453, 1989
22. Kittleson MD, Thomas W, Loyer C, Kienle R. Balloon dilatation caused death of two bulldogs with pulmonic stenosis and single coronary artery; Letter. J Vet Intern Med 6:250, 1992
23. Jacobs G, Mahaffey M, Rawlings CA. Valvular pulmonic stenosis in four Boykin Spaniels. J Am Anim Hosp Assoc 26:247, 1990
24. Patterson DF, Haskins ME, Schnarr WR. Hereditary dysplasia of the pulmonary valve in Beagle dogs. Am J Cardiol 47:631, 1981
25. Malik R, Church DB, Hunt GB. Valvular pulmonic stenosis in Bullmastiffs. J Small Anim Pract 34:288, 1993

25a. Brown WA. Ventricular septal defects in the English Springer Spaniel. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XII. Philadelphia, WB Saunders, 1995, p 827

26. Liu SK, Tilley LP. Dysplasia of the tricuspid valve in the dog and cat. J Am Vet Med Assoc 169:623, 1976
27. Hamlin RL, Harris SG. Mitral incompetence in Great Dane pups. J Am Vet Med Assoc 154:790, 1969
28. Liu SK, Tilley LP. Malformation of the canine mitral valve complex. J Am Vet Med Assoc 167:465, 1975
29. Lehmkuhl LB, Ware WA, Bonagura JD. Mitral stenosis in 15 dogs. J Vet Intern Med 8:2, 1994
30. Fox PR, Miller MW, Liu SK. Clinical, echocardiographic, and Doppler imaging characteristics of mitral valve stenosis in two dogs. J Am Vet Med Assoc 201:1575, 1992
31. Malik R, Church DB. Congenital mitral insufficiency in bull terriers. J Small Anim Pract 29:549, 1988
32. Zook BC. Congenital cardiovascular defects. *In* Holzworth J (ed): Diseases of the Cat: Medicine and Surgery. Philadelphia, WB Saunders, 1987, p 820
33. Thrusfield MV, Aitken CGG, Darke PGG. Observations on breed and sex in relation to canine heart valve incompetence. J Small Anim Pract 26:709, 1985
34. Darke PGG. Valvular incompetence in cavalier King Charles Spaniels. Vet Rec 120:365, 1987
35. Haggstrom J, Hansson K, Kvart C, Swenson L. Chronic valvular disease in the cavalier King Charles Spaniel in Sweden. Vet Rec 131:549, 1992
36. Beardow AW, Buchanan JW. Chronic mitral valve disease in cavalier King Charles Spaniels: 95 cases (1987–1991). J Am Vet Med Assoc 202:1023, 1993
37. Malik R, Hunt GB, Allan GS. Prevalence of mitral valve insufficiency in cavalier King Charles Spaniels. Vet Rec 130:302, 1992
38. Buchanan JW, Kelly AM. Endocardial splitting of the left atrium in the dog with hemorrhage and hemopericardium. J Am Vet Radiol Soc 5:28, 1964
39. Tashjian RJ, Das KM, Palich WE, et al. Studies on cardiovascular disease in the cat. Ann NY Acad Sci 127:581, 1965

40. Hubben K, Patterson DF, Botts RP. Telangiectasis in canine heart valves. Zentralbl Veterinarmed A 10:1935, 1963
41. Takeda T, Makita T, Nakamura N, Kimizuka G. Morphologic aspects and morphogenesis of blood cysts on canine cardiac valves. Vet Pathol 28:16, 1991
42. Lombard CW, Buergelt CD. Vegetative bacterial endocarditis in dogs; Echocardiographic diagnosis and clinical signs. J Small Anim Pract 24:325, 1983
42a. Sisson D. Bacterial Endocarditis. The 18th Annual Waltham/OSU Symposium for the Treatment of Small Animal Diseases, 1994, p 79
43. Calvert CA, Greene CE, Hardie EM. Cardiovascular infections in dogs: Epizootiology, clinical manifestations, and prognosis. J Am Vet Med Assoc 187:612, 1985
44. Anderson CA, Dubielzig RR. Vegetative endocarditis in dogs. J Am Anim Hosp Assoc 20:149, 1984
45. Bennett D, Taylor DJ. Bacterial endocarditis and inflammatory joint disease in the dog. J Small Anim Pract 29:347, 1988
46. Elwood CM, Cobb MA, Stepien RL. Clinical and echocardiographic findings in 10 dogs with vegetative bacterial endocarditis. J Small Anim Pract 34:420, 1993
47. Takahashi T, Tamura Y, Yoshimura H, et al. *Erysipelothrix tonsillarum* isolated from dogs with endocarditis in Belgium. Res Vet Sci 54:264, 1993
48. Van Vleet JF, Ferrans VJ. Myocardial diseases of animals. Am J Pathol 124:98, 1986
49. Sisson DD, Thomas WP. Myocardial diseases of the dog and cat. *In* Ettinger SJ, Feldman E (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1994, p 995
50. Calvert CA. Dilated congestive cardiomyopathy in Doberman pinschers. Compend Cont Educ 8:417, 1986
51. Harpster NK. Boxer cardiomyopathy. A review of the long-term benefits of antiarrhythmic therapy. Vet Clin North Am 21:989, 1991
52. Thomas RE. Canine idiopathic congestive cardiomyopathy—breed incidence from a series of 17 cases. Vet Rec 121:423, 1987
53. Tidholm A. Dilated cardiomyopathy in the Newfoundland dog: A study of 118 cases. Proceedings, 12th Annual Meeting of the European Society of Veterinary Cardiology, 1993, p 12
54. Gooding JP, Robinson WF, Mews GC. Echocardiographic characterization of dilatation cardiomyopathy in the English Cocker Spaniel. Am J Vet Res 47:1978, 1986
55. Moise NS, Valentine BA, Brown CA, et al. Duchenne's cardiomyopathy in a canine model: Electrocardiographic and echocardiographic studies. J Am Coll Cardiol 17:812, 1991
56. Thomas WP. Myocardial diseases of the dog. *In* Bonagura JD (ed): Cardiology. New York, Churchill Livingstone, 1987, p 117
57. Sisson DD. Heritability of idiopathic myocardial hypertrophy and dynamic subaortic stenosis in Pointer dogs. J Vet Intern Med 4:118, 1990
58. Mauldin GE, Fox PR, Patnaik AK, et al. Doxorubicin-induced cardiotoxicosis: Clinical features in 32 dogs. J Vet Intern Med 6:82, 1992
59. Page RL, Keene BW. Doxorubicin cardiomyopathy. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 783
60. Waldvogel AS, Hassam S, Weilenmann R, et al. Retrospective study of myocardial canine parvovirus infection by in-situ hybridization. J Vet Med Series B 38:353, 1992
61. Henes MG. Myocardial dysfunction associated with Lyme disease. Vet Med 84:982, 1989
62. Keene BW. Canine cardiomyopathy. *In* Kirk RW (ed): Current Veterinary Therapy X. Philadelphia, WB Saunders, 1989, p 241
63. Barr SC, Simpson RM, Schmidt SP, et al. Chronic dilatative myocarditis caused by *Trypanosoma cruzi* in two dogs. J Am Vet Med Assoc 195:1237, 1989
64. Atkins CE, Gallo AM, Kurzman ID, Cowen P. Risk factors, clinical signs and survival in cats with a clinical diagnosis of idiopathic hypertrophic cardiomyopathy: 74 cases (1985–1989). J Am Vet Med Assoc 201:613, 1992
65. Broussard JD, Peterson ME, Fox PR. Changes in the clinical and laboratory findings in hyperthyroid cats from 1982–1992. J Am Vet Med Assoc 206:302, 1995
66. Stalis IH, Bossbaly MJ, Van Winkle TJ. Feline endomyocarditis and left ventricular endocardial fibrosis. Vet Pathol 32:122, 1995
67. Bossbaly MJ, Stalis IH, Knight DH, Van Winkle TJ. Feline endomyocarditis: A clinical/pathologic study of 44 cases; abstract. J Vet Intern Med 8:144, 1994
68. Skiles ML, Pion PD, Hird DW, et al. Epidemiologic evaluation of taurine deficiency and dilated cardiomyopathy in cats. J Vet Intern Med 4:117, 1990
69. Sisson DD, Knight DH, Helenski C, et al. Plasma concentrations and M-mode echocardiographic measures in healthy cats and in cats with dilated cardiomyopathy. J Vet Intern Med 5:232, 1991
70. Skrodzki M, Trautvetter E, Monch E. Plasma taurine levels in healthy cats and cats with cardiac disorders. J Nutr 121:S171, 1991
71. Lawler DF, Templeton AJ, Monti KL. Evidence for genetic involvement in feline dilated cardiomyopathy. J Vet Intern Med 7:383, 1993
72. Dow SW, Fettman MJ, Smith KR, et al. Taurine depletion and cardiovascular disease in adult cats fed a potassium-depleted acidified diet. Am J Vet Res 53:402, 1992
73. Liu SK: Left ventricular false tendons associated with cardiac malfunction in 101 cats. Lab Invest 56:44A, 1987
74. Lombard CW, Buergelt CD. Endocardial fibroelastosis in four dogs. J Am Anim Hosp Assoc 20:271, 1984
75. Zook BC, Paasch LH, Chandra RS, et al. The comparative pathology of primary endocardial fibroelastosis in Burmese cats. Virchows Arch A 390:211, 1981
76. Hamlin RL, Smetzer DL, Bresnock EM. Sinoatrial syncope in Miniature Schnauzers. J Am Vet Med Assoc 161:1022, 1972
77. Moise NS, Gilmour RF. Inherited sudden cardiac death in German Shepherds. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 749
78. Moise NS, Meyers-Wallen V, Flahive WJ, et al. Inherited ventricular arrhythmias and sudden death in German shepherd dogs. J Am Coll Cardiol 24:233, 1994
79. James TN, Robertson BT, Waldo AL, et al. Hereditary stenosis of the His bundle in Pug dogs. Circulation 52:1152, 1975
80. James TN, Drake EA. Sudden death in Doberman pinschers. Ann Intern Med 68:821, 1968
81. Jeraj K, Ogburn PN, Edwards WD, et al. Atrial standstill, myocarditis, and destruction of cardiac conduction system. Clinicopathologic correlation in a dog. Am Heart J 99:185, 1980
82. Bonagura JD, O'Grady M. ECG of the month. J Am Vet Med Assoc 183:658, 1983
83. Tilley LP, Liu SK. Persistent atrial standstill in the dog and cat. Proceedings, American College of Veterinary Internal Medicine, 1983, p 43

84. Childers HE. Atrial Standstill in a dog. J Am Vet Med Assoc 188:140, 1986
85. Brownlie SE. An electrocardiographic survey of cardiac rhythm in Irish Wolfhounds. Vet Rec 129:470, 1991
86. Brownlie SE, Nott H. An investigtion of size in Irish wolfhounds with supraventricular cardiac arrhythmias. Vet Rec 129:493, 1991
87. Bohn FK, Patterson DF, Pyle RL. Atrial fibrillation in dogs. Br Vet J 127:485, 1971
88. Bonagura JD, Ware WA. Atrial fibrillation in the dog. Clinical findings in 81 cases. J Am Anim Hosp Assoc 22:111, 1986
89. Bokenhans R. Fibrilacion auricular en caninos. Distribucion segun sexo, edad y talla de 100 casos. (Auricular fibrillation in dogs. Distribution by sex, age and height in 100 cases). Rev Med Vet 73:66, 1992
90. Berg RJ, Wingfield W. Pericardial effusion in the dog: A review of 42 cases. J Am Anim Hosp Assoc 20:721, 1984
91. Cobb MA, Brownlie SE. Intrapericardial neoplasia in 14 dogs. J Small Anim Pract 33:309, 1992
92. Holt D, Van Winkle T, Schelling C, Prymak C. Correlation between thoracic radiographs and postmortem findings in dogs with hemangiosarcoma: 77 cases (1984–1989). J Am Vet Med Assoc 200:1535, 1992
93. Sisson D, Thomas WP, Ruehl WW, Zinkl JG. Diagnostic value of pericardial fluid analysis in the dog. J Am Vet Med Assoc 184:51, 1984
94. Kleine LJ, Zook BC, Munson TO. Primary cardiac hemangiosarcomas in dogs. J Am Vet Med Assoc 157:326, 1970
95. Aronsohn M. Cardiac hemangiosarcoma in the dog. J Am Vet Med Assoc 187:922, 1985
96. Fruchter AM, Miller CW, O'Grady MR. Echocardiographic results and clinical considerations in dogs with right atrial/auricular masses. Can Vet J 33:171, 1992
97. Hayes HM, Sass B. Chemoreceptor neoplasia: A study of the epidemiological features of 357 canine cases. J Vet Intern Med 35:401, 1988
98. Guarda F, Bussadori C, Scotti C, et al. Patologia dei tumori della base del cuore (HBT) nel cane. (Pathology of canine heart base tumors). Veterinaria 6:31, 1992
99. Bossbaly MJ, Buchanan JW, Sammarco C. Aortic body carcinoma and myocardial infarction in a Doberman pinscher. J Small Anim Pract 34:638, 1993
100. Rush JE, Keene BW, Fox PR. Pericardial disease in the cat: A retrospective evaluation of 66 cases. J Am Anim Hosp Assoc 26:39, 1990
101. Tilley LP, Bond B, Patnaik AK, Liu SK. Cardiovascular tumors in the cat. J Am Anim Hosp Assoc 17:1009, 1981
102. Kume S, cited by Rawlings CA. Pulmonary arteriography and hemodynamics during feline heartworm disease. J Vet Intern Med 4:285, 1990
103. LaRue MJ, Murtaugh RJ. Pulmonary thromboembolism in dogs: 47 cases (1986–1987). J Am Vet Med Assoc 197:1368, 1990
104. Van Winkle TJ, MacDonald M, Hendricks J. Thrombosis of the portal vein, pulmonary arteries, and aorta in the dog; Abstract. Proceedings, 40th Annual American College of Veterinary Pathology, 1989
105. Van Winkle TJ, Bruce E. Thrombosis of the portal vein in 11 dogs. Vet Pathol 30:28, 1993
106. Rogers WA, Bishop SP, Rohovsky MW. Pulmonary artery medial hypertrophy and hyperplasia in conventional and specific pathogen free cats. Am J Vet Res 32:767, 1971
107. Liu SK, Tilley LP, Tappe JP, Fox PR. Clinical and pathologic findings in dogs with atherosclerosis: 21 cases (1970–1983). J Am Vet Med Assoc 189:227, 1986
108. Detweiler DK. Spontaneous and induced arterial disease in the dog: Pathology and pathogenesis. Toxicol Pathol 17:94, 1989
109. Hartman HA. Idiopathic extramural coronary arteritis in Beagle and mongrel dogs. Vet Pathol 24:537, 1987
110. Spencer A, Greaves P. Periarteritis in a Beagle colony. J Comp Pathol 97:121, 1987
111. Scott-Moncrieff JC, Snyder PW, Glickman LT, Felsburg PJ. Systemic necrotizing vasculitis (juvenile polyarteritis syndrome) in nine young laboratory beagles. J Am Vet Med Assoc 201:1553, 1992
112. Felsburg PJ, HogenEsch H, Somberg RL, et al. Immunologic abnormalities in canine juvenile polyarteritis syndrome: A naturally occurring animal model of Kawasaki disease. Clin Immunol Immunopathol 65:110, 1992
113. Suter PF, Fox PR. Peripheral vascular disease. *In* Ettinger SJ, Feldman E (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 1068
114. Buchanan JW, Baker GJ, Hill JD. Aortic embolism in cats: Prevalence, surgical treatment and electrocardiography. Vet Rec 79:496, 1966
115. Littman MP. Spontaneous systemic hypertension in 24 cats. J Vet Intern Med 8:79, 1994
116. Vincent IC, Michell AR, Lehy RA. Non-invasive measurement of arterial blood pressure in dogs: A potential indicator for the identification of stress. Res Vet Sci 54:195, 1993
117. Bovee KC, Papanek PE, Skelton MM, et al. Lability of blood pressure in genetically hypertensive dogs using 24-hour monitoring. J Vet Intern Med 6:116, 1992
118. Littman MP, Robertson JL, Bovee KC. Spontaneous systemic hypertension in dogs: Five cases (1981–1983). J Am Vet Med Assoc 193:486, 1988
119. Remillard RL, Ross JN, Eddy JB. Variance of indirect blood pressure measurements and prevalence of hypertension in clinically normal dogs. Am J Vet Res 52:561, 1991
120. Detweiler DK, Cox RH, Alonso R, et al. Hemodynamic characteristics of the young adult Greyhound. Fed Proc 34:360, 1974

24

Congenital Heart Disease

JOHN D. BONAGURA
LINDA B. LEHMKUHL

CAUSES OF CARDIAC MALFORMATIONS

Congenital heart disease (CHD) is a clinically significant cause of cardiovascular morbidity and mortality in small animals.[1–12] Etiologies, developmental lesions, pathophysiology, and clinical findings are often similar to those reported in humans with cardiac malformations.[13, 14, 14a]

Congenital cardiac defects may develop as a result of genetic, environmental, chromosomal, infectious, toxicologic, nutritional, and drug-related factors.[11, 12, 15–20] Surveys of cats suggest that some breeds are predisposed to certain malformations, but more is known about genetically transmitted defects in specific canine breeds (Table 24–1).[2, 21, 22] There is little data regarding nongenetic factors pertaining to spontaneous CHD in the dog and cat.

A genetic basis has been demonstrated for some CHD in the dog. Earlier studies suggested a polygenic model of transmission in which multiple genes have additive effect and produce a discrete phenotypic trait once a "threshold" has been attained. Studies by Patterson et al[25] suggest a single major gene effect with superimposed variation possibly related to other gene loci or the environment. Such patterns of inheritance explain the spectrum of subclinical to severe malformations found in families of dogs with CHD. The precise mechanisms by which parents with apparently normal phenotype produces offspring with CHD has not been completely elucidated. Unfortunately, since simple (Mendelian) genetic transmission is not causative, it is difficult to provide genetic counseling for breeders. Moreover, it may be hard to eliminate or reduce the prevalence of cardiac defects without careful attention to pedigree and breeding trials.

PREVALENCE

The exact prevalence of CHD is uncertain as there are both national and regional breed differences for certain cardiovascular malformations (chapter 23). A compilation of congenital heart defects in the United States has been reported in dogs and cats,[2, 5, 8, 22] and common defects are summarized in Tables 23–4, 23–5, and Table 24–2. Because multiple congenital anomalies may be identified in some animals,[27–32] the chosen method of reporting defects will alter frequency data slightly.

In one of the largest canine surveys, 325 malformations were detected in

TABLE 24–1
Breed Predispositions to Congenital Heart Disease

Breed	Malformation
Airedale terrier	Pulmonic stenosis (PS)
Beagle	Pulmonic stenosis, pulmonary insufficiency
Bichon frise	Patent ductus arteriosus (PDA)
Bouvier de Flandres	Subaortic stenosis
Boykin spaniel	Pulmonic stenosis
Boxer	Subaortic stenosis (SAS), pulmonic stenosis, atrial septal defect (ASD)
Bull terrier	Mitral valve dysplasia, aortic stenosis
Chihuahua	Patent ductus arteriosus, pulmonic stenosis
Cocker spaniel	Patent ductus arteriosus, pulmonic stenosis
Collie	Patent ductus arteriosus
Doberman pinscher	Atrial septal defect
English bulldog	Pulmonic stenosis, tetralogy of Fallot, ventricular septal defect (VSD), subaortic stenosis
English springer spaniel	Patent ductus arteriosus, ventricular septal defect
German shepherd	Patent ductus arteriosus, subaortic stenosis, mitral valve dysplasia, tricuspid valve dysplasia, tricuspid valve dysplasia, persistent right aortic arch
German shorthair pointer	Subaortic stenosis
Golden retriever	Subaortic stenosis, mitral valve dysplasia, tricuspid valve dysplasia
Great Dane	Mitral valve dysplasia, tricuspid valve dysplasia, aortic stenosis, persistent right aortic arch
Irish setter	Persistent right aortic arch
Kerry blue terrier	Patent ductus arteriosus
Keeshond	Tetralogy of Fallot, ventricular septal defect, patent ductus arteriosus
Labrador retriever	Tricuspid valve dysplasia, patent ductus arteriosus
Maltese	Patent ductus arteriosus
Mastiff	Mitral valve dysplasia, pulmonic stenosis
Newfoundland	Subaortic stenosis, mitral dysplasia, patent ductus arteriosus
Old English sheepdog	Tricuspid valve dysplasia
Poodle breeds	Patent ductus arteriosus
Pomeranian	Patent ductus arteriosus
Rottweiler	Aortic stenosis
Samoyed	Pulmonic stenosis, aortic stenosis, ? atrial septal defect
Schnauzer breeds	Pulmonic stenosis
Shetland sheepdog	Patent ductus arteriosus
Terrier breeds	Pulmonic stenosis
Weimaraner	Tricuspid valve dysplasia, peritoneopericardial diaphragmatic hernia
West Highland white terrier	Pulmonic stenosis, ? VSD
Yorkshire terrier	Patent ductus arteriosus

290 dogs, and the overall prevalence in a university hospital canine population was 6.8 per 1000 dogs.[5] In these 290 dogs, congenital disorders included patent ductus arteriosus (28 percent), pulmonic stenosis (20 percent), aortic stenosis (14 percent), persistent right aortic arch (8 percent), ventricular septal defect (7 percent), and in less than 5 percent, tetralogy of Fallot, persistent left cranial vena cava, and atrial septal defects. In a 1989 unpublished survey of congenital cardiac defects from the United Kingdom, 32 percent of 339 reported cases were due to subaortic stenosis; 20 percent, patent ductus arteriosus; 14 percent, mitral dysplasia; 12 percent, pulmonic stenosis; and 8 percent, ventricular septal defects. More recent reports,[33, 34] including a large study by Buchanan that included prevalence information from a North American data base of over 1300 cases,[34] indicated that while patent ductus arteriosus is still the most frequently reported lesion (31.7 percent), subaortic stenosis (22.1 percent) now exceeded pulmonic stenosis (18.3 percent) in prevalence. Based on these studies, the overall prevalence of canine congenital heart disease ranges from 0.46 percent to 0.85 percent of university hospital admissions.

In cats, the estimated prevalence of congenital heart disease using pooled data was between 2 and 10 cats per 1000 admissions (0.2 to 1 percent). A total of 287 anomalies was recorded,[8, 22] including atrioventricular septal defects (comprising ventricular septal defect, atrial septal defect, and endocardial cushion defect—approximately 24 percent), atrioventricular valve dysplasia (17 percent), endocardial fibroelastosis (11 percent), patent ductus arteriosus (11 percent), aortic stenosis (6 percent), and tetralogy of Fallot (6 percent).

CLINICAL EVALUATION OF CONGENITAL HEART DISEASE

Identification of congenital heart disease is always important in newly acquired pets and in animals raised for breeding. Accurate assessment may require Doppler echocardiography and cardiac catheterization. The practitioner should be familiar with common cardiac malformations, associated clinical findings, and the underlying genetic basis when known.

TABLE 24–2
Classification of Congenital Heart Disease

Ventricular Outflow Obstruction
- Right-sided
  - Pulmonic stenosis
    - Valvular dysplasia*
    - Subvalvular
    - Supravalvular
  - Tetralogy of Fallot* (see below)
  - Double-chambered right ventricle
- Left-sided
  - Aortic stenosis
    - Subvalvular (subaortic)*
      - Discrete
      - Fibromuscular
      - Dynamic
    - Valvular
    - Supravalvular
  - Coarctation of the aorta
  - Hypoplasia of the aorta
  - Interruption of the aorta

System to Pulmonary Shunting (Left-to-Right)
- Atrial septal defect (ASD)*
  - Patent foramen ovale
  - Secundum defect
  - Primum defect
  - Sinus venosus defect
- Atrioventricular septal defects/endocardial cushion defect*
  - Incomplete or partial
  - Common atrioventricular canal
- Anomalous pulmonary venous return
- Ventricular septal defects (VSD)*
  - Perimembranous defects (subcristal)
  - Muscular defects
  - Subpulmonic (supracristal) defects
- Patent ductus arteriosus (PDA)*
- Aorticopulmonary septal defect (see Vascular anomalies)
- Truncus arteriosus
- Systemic arterial to pulmonary shunts

Pulmonary to Systemic Shunting (Right-to-Left)
- Pulmonary stenosis or tricuspid valve dysplasia with patent foramen ovale
- Tricuspid atresia
- Tetralogy of Fallot*
- Pulmonary atresia
- Eisenmenger's physiology (reversed shunting across a septal defect or PDA)

Malformation of the Atrioventricular Valves
- Mitral valve dysplasia
  - Insufficiency
  - Stenosis
- Tricuspid valve malformation
  - Insufficiency
  - Stenosis
  - Atresia (see above)

Transposition Complexes
- Anomalous pulmonary venous connection
- Double-outlet right ventricle
- Transposition of the great vessels
  - D-transposition
  - L-transposition (congenitally corrected)

Miscellaneous Cardiac Defects
- Anomalous development of the atria
  - Cor triatriatum
  - Cor triatriatum dexter
- Endocardial fibroelastosis
- Cordis ectopia

Multiple Cardiac Anomalies

Vascular Anomalies
- Persistent patent ductus arteriosus* (see above)
- Vascular "ring" anomalies
  - Persistent right fourth aortic arch*
  - Left aortic arch with right ligamentum arteriosum
  - Double aortic arch
  - Retroesophageal subclavian artery
- Anomalies of the aorta and related arteries (also, ventricular outflow obstruction, above)
- Venous anomalies
  - Persistent left cranial vena cava

Pericardial Defects
- Congenital peritoneopericardial diaphragmatic hernia*
- Pericardial cyst
- Incomplete (partial absence of the) pericardium

*One of the most frequently recognized malformations. National and regional differences are recognized. Overall, patent ductus arteriosus, subaortic stenosis, pulmonic stenosis, ventricular septal defect, and atrioventricular valvular dysplasia are the most frequently recognized lesions in dogs. Ventricular septal defect and mitral valve malformation are the most frequently recognized cardiac malformations in cats.

Knowledge of the breed is particularly important (chapter 23) because a genetic basis is suspected for many of the cardiac malformations (see Table 24–1). A diagnosis can usually be attained by a complete noninvasive evaluation that includes the history, physical examination, thoracic radiography, electrocardiography, routine hematologic tests, and echocardiography (chapters 4 through 8). Definitive diagnosis requires Doppler echocardiography or, infrequently, cardiac catheterization and angiocardiography.

HISTORY AND PHYSICAL EXAMINATION

INNOCENT MURMURS

Normal puppies and kittens can exhibit *innocent systolic cardiac murmurs,* which must be distinguished from murmurs caused by a cardiac malformation. The typical innocent murmur is soft (grade 1 to 3/6) and is usually described as loudest over or craniodorsal to the pulmonic or aortic valve area; protomesosystolic (or ejection) in timing; variable with heart rate and changing body position; often musical in quality; and typically diminishing in intensity or resolved by 16 weeks of age.

CONGENITAL CARDIAC MURMURS

In contrast, murmurs of congenital cardiac origin are often moderately intense to loud. There are occasional exceptions; for example, a heart murmur may not be audible with very large defects, even in the presence of severe cyanotic heart disease; puppies with

tricuspid valve dysplasia may have severe malformation and a relatively soft right-sided heart murmur; and mild stenosis of a semilunar valve or ventricular outflow tract may generate only a soft, systolic murmur that can be easily confused with an innocent flow murmur. Murmurs of outflow tract obstruction also may increase in intensity with increasing sympathetic activity or heart rate as do innocent murmurs.

The presence of any type or grade of heart murmur in a young animal should be considered as potentially compatible with a diagnosis of congenital heart disease. Usually, a *precordial thrill* accompanies loud murmurs, and this vibration corresponds to the point of maximal murmur intensity. The location of a precordial thrill often is characteristic of the associated lesion. Additional auscultatory abnormalities may be present, such as a loud or split second heart sound.

AGE

Age is a factor when assessing the effect of pulmonary vascular resistance on the magnitude of systemic-to-pulmonary shunts. Although the pulmonary vascular resistance and right ventricular pressures fall immediately at birth, they continue to decline during the first 1 to 2 months of life,[35] and left-to-right shunting may not be fully manifested until a number of weeks after birth. Some lesions may progress with age. For example, congenital subaortic stenosis may actually develop during the first 2 months of life, and the associated cardiac murmur increases in intensity as the dog grows to maturity.[18, 35a] A progression of clinical signs with increasing age is to be expected in animals with severe malformations. Innocent murmurs are most common in puppies less than 16 weeks old.

GENDER

A sex predisposition is not well established in dogs. Exceptions include the higher prevalence of patent ductus arteriosus in female dogs, and the possible male predominance of both tricuspid dysplasia in dogs and pulmonic stenosis in English bulldogs.[9, 34] The Siamese and Burmese breeds may be predisposed to some congenital heart defects, and male kittens seem to be at higher risk for cardiac malformation.[22]

CLINICAL SIGNS

Affected animals may fail to grow; exhibit shortness of breath, cough, abdominal distention, cyanosis, weakness, syncope, or seizures; or die suddenly. Many are relatively asymptomatic until acute decompensation occurs. Whereas some pets with congenital heart disease are examined for clinical signs related to their malformation, most cases are identified at the time of immunization following auscultation of a cardiac murmur.

OTHER PHYSICAL EXAMINATION FINDINGS

Abnormalities of the arterial pulse, mucous membranes, jugular venous pulse, or precordium may support a clinical suspicion of congenital disease. *Hyperkinetic ("water-hammer") arterial pulsations* are characteristic of lesions causing abnormal diastolic runoff of aortic blood as occurs with patent ductus arteriosus or aortic regurgitation. *Hypokinetic arterial pulses* are typical of severe subaortic stenosis or tricuspid dysplasia and are characterized by delayed ventricular ejection or diminished output, respectively. Although *cyanosis* often indicates right-to-left shunting, this sign also can develop with severe congestive failure and secondary pulmonary dysfunction. Prominent *jugular venous pulsations* may suggest a right heart abnormality, such as pulmonic stenosis or severe tricuspid regurgitation. A *precordial heave* (prominent apical impulse) often indicates hypertrophy or enlargement of the underlying ventricle.

CARDIAC IMAGING

Survey thoracic radiographs are important to identify cardiomegaly, enlargement of the great vessels, pulmonary circulatory dynamics, and congestive heart failure. Angiocardiography characterizes anatomic defects and delineates abnormal blood flow. Echocardiography noninvasively defines anatomic lesions and abnormal blood flow patterns and estimates ventricular function. Nuclear medicine studies, computed tomography, and magnetic resonance imaging have specific applications but are limited in availability.

SURVEY RADIOGRAPHY

Radiography plays an integral role in evaluation for congenital heart disease.[4, 36–38] Radiographic assessment of cardiomegaly ideally should be done in conjunction with the electrocardiogram (ECG) and preferably the echocardiogram.

CARDIOMEGALY. The detection of cardiomegaly is relatively easy. However, the distinction between right and left ventricular enlargement may be difficult without echocardiography, and the frequent occurrence of apex shifting may also confuse the clinician and result in erroneous diagnosis. There is a tendency to overinterpret the right ventricle in neonates, in which some right ventricular dominance is normal. The thoracic radiograph is a fairly good indicator of the severity of congenital heart disease when the underlying condition is characterized by left-to-right shunting or valvu-

lar insufficiency. Thus, a small ventricular septal defect or mildly dysplastic tricuspid valve is likely to be associated with mild cardiomegaly, whereas a severe defect is generally characterized by severe heart enlargement. However, in cases of outflow obstruction, pulmonary hypertension, or right-to-left shunts, lesion severity is often not accurately reflected in the degree of radiographic cardiomegaly; ventricular hypertrophy is often concentric (compromising the lumen) and is far better appreciated by echocardiography.

GREAT VESSELS. Dilation of the great vessels can provide clues to underlying cardiac malformations. Aortic widening in the cranial mediastinum is typical of the poststenotic dilatation of subaortic stenosis; the aortic anomaly is sometimes noted with tetralogy of Fallot. Aneurysmal dilation of the descending aorta is common with patent ductus arteriosus. Enlargement of the main pulmonary artery may accompany poststenotic turbulent flow from pulmonic stenosis, increased flow caused by any left-to-right shunt, or pulmonary hypertension. Caudal vena cava enlargement may be noted in tricuspid dysplasia, pulmonic stenosis, or cor triatriatum dexter.

PULMONARY VASCULARITY. Although changes must be assessed with caution, pulmonary vascularity serves as a useful guideline in determining pulmonary overcirculation, undercirculation, and venous congestion.[4, 36–38] Cranial and caudal lobar arteries and veins, as well as peripheral pulmonary vascular markings, should be examined. Right-to-left shunts, like tetralogy of Fallot, are characterized by diminished peripheral perfusion and normal-to-small lobar vessels. Reversed or bidirectional shunts resulting from pulmonary hypertension may cause diminished peripheral perfusion, dilated lobar arteries, and a dilated main pulmonary trunk. In some cases of reversed shunting, however, the pulmonary vasculature seems remarkably normal. Vascularity can also be decreased in other conditions, such as pulmonic stenosis and severe tricuspid dysplasia. Conversely, left-to-right shunts, like atrioventricular septal defects and patent ductus arteriosus, have an increased dimension of lobar arteries and veins, with prominent peripheral vascular markings that may be misinterpreted as interstitial lung densities. Right or left ventricular congestive failure may be heralded by widened diameter of the caudal vena cava or pulmonary veins, respectively.

ANGIOGRAPHY

Selective angiocardiography identifies most of the common congenital heart defects.[30, 37, 39–45] A general approach is to perform both a right and left ventriculogram and to record the movement of injected contrast material over 10 to 20 seconds. A supravalvular aortic injection is also performed, and the movement of blood is followed for 8 to 10 seconds.

RIGHT VENTRICULOGRAM. The following lesions can generally be identified: tricuspid regurgitation, double-chambered right ventricle or anomalous fibromuscular bands, pulmonary stenosis or atresia, right-to-left–shunting ventricular septal defect, tetralogy of Fallot (and pseudotruncus arteriosus), double-outlet right ventricle, transposition of the great vessels, truncus arteriosus, aorticopulmonary communication (with pulmonary hypertension), reversed patent ductus arteriosus, and abnormal pulmonary vascularity owing to pulmonary hypertension or vascular disease. Following return of contrast to the left side of the heart from the right ventricular (or pulmonary artery) injection, the following lesions can generally be identified: anomalous pulmonary venous return (to the right atrium), atrial septal defect (left-to-right shunting), mitral stenosis, and subaortic and aortic valve stenosis.

LEFT VENTRICULOGRAM. The following lesions can usually be identified: mitral regurgitation; ventricular septal defect (left-to-right shunting); subaortic, aortic valvular, and supravalvular stenosis; truncus arteriosus (and pseudotruncus arteriosus); and supravalvular lesions listed later under the aortogram.

AORTIC INJECTION. This generally delineates aortic regurgitation; prolapse of an aortic valve leaflet into a ventricular septal defect; abnormal coronary arteries; aorticopulmonary communication (left-to-right shunting); coarctation, hypoplasia, or interruption of the aorta; abnormalities of the aortic arch or branches; patent ductus arteriosus (left-to-right shunting); and abnormal pulmonary collateral circulation (bronchoesophageal circulation).

ADDITIONAL INJECTIONS. Injection of contrast into the left jugular vein identifies persistent left cranial vena cava. A right atrial injection is needed to document a right-to-left shunting atrial septal defect or hypoplasia/atresia of the tricuspid valve and right ventricle. A caudal vena caval injection will best delineate a partitioned right atrium, as in cor triatriatum dexter. Abnormal position of the angiocardiographic catheter may also delineate a lesion, as when an atrial septal defect is crossed.

ECHOCARDIOGRAPHY

Echocardiography permits detailed imaging of cardiac anatomy. When combined with Doppler echocardiographic studies, blood flow can be detected and intravascular pressures estimated (chapter 8).[21, 44, 46–52] Quantifying pressure gradients across semilunar valves requires continuous-wave Doppler techniques.[48, 51, 53]

Contrast echocardiography, in which intravascular echo targets are created by the rapid injection of agitated saline or indocyanine-green dye, can reliably detect some intracardiac (particularly right-to-left) shunts, as can color-flow Doppler echocardiography (see Figs. 8–2, 8–3).

Information obtained from a careful echocardiographic and Doppler echo study should include (1) anatomic detail, cardiac function, and cardiac dimensions determined by two-dimensional and M-mode echo; (2) detection of abnormal blood flow by pulsed-wave or color-coded Doppler or through contrast echocardiography; (3) identification of turbulent or high-velocity blood flow in the heart and great vessels, using pulsed-wave Doppler echo; and (4) quantifying high-velocity flow by continuous-wave Doppler echo. Velocity data from the continuous wave study can be used to measure pressure gradients by means of the modified Bernoulli equation, in which the instantaneous pressure drop across a stenosis or shunt is estimated by

$$\text{Pressure gradient (mm Hg)} = 4 \times \text{peak velocity (m/s)}^2$$

It is also possible to estimate pulmonary artery pressures, shunt ratio, and regurgitant fraction using Doppler techniques. Estimates of pulmonary arterial pressures usually involve measuring the peak velocity of any recorded pulmonary insufficiency or tricuspid regurgitation (in the absence of pulmonic stenosis or a large ventricular septal defect) and employing the Bernoulli equation. The greater the pressure in the pulmonary artery, the higher the velocity of regurgitation. Shunts are estimated noninvasively by measuring systemic flow and pulmonary flow using pulsed Doppler or color-flow convergence techniques.[54, 55]

ELECTROCARDIOGRAPHY

The ECG is often helpful in the diagnosis of congenital heart disease.[4, 7, 35, 38, 56] A normal ECG does not rule out a cardiac malformation, but an abnormal ECG helps indicate the cause. Persistence of a right ventricular hypertrophy pattern after the first few weeks of age in the dog is abnormal and highly suggestive of pulmonic stenosis, tetralogy of Fallot, tricuspid dysplasia, atrial septal defect, large ventricular septal defect, or pulmonary hypertension. Right ventricular hypertrophy can also lead to conduction delay, with right axis deviation and QRS complex widening. Occasionally, the presence of congenital right bundle branch block may suggest an erroneous diagnosis of right ventricular hypertrophy in an animal with a left-sided heart lesion, but as a general rule, this finding indicates one of the aforementioned right-sided defects. Increased QRS voltages with a normal frontal axis are typical of patent ductus arteriosus and other defects causing left ventricular enlargement. Left axis deviation in the frontal plane may indicate left ventricular hypertrophy or left anterior fascicular block.

CARDIAC CATHETERIZATION

Cardiac catheterization is an invasive procedure useful for diagnosing structural cardiovascular malformation and assessing physiologic associated derangements.[4, 40–43, 57–60, 60a] It permits (1) oximetry (sampling for hemoglobin-oxygen saturation), (2) cardiac output and stroke volume measurements, (3) indicator dilution studies, and (4) intravascular and intracardiac pressure recording. Selective angiocardiograms with catheterization data represent the "gold standard" by which to compare other diagnostic and hemodynamic assessments. A complete description of cardiac catheterization can be found in chapter 9.

PRESSURE GRADIENTS AND VALVE STENOSIS. Blood is normally propelled across the heart by the generation of small, instantaneous pressure gradients, although peak pressures should be equal across a normal opened cardiac valve. Valve stenosis is associated with an increased velocity flow. This is caused by development of a *pressure gradient*—an increase in pressure behind the stenosis, relative to the pressure distal to the valve. This pressure gradient can be measured as an instantaneous, peak-to-peak, or mean pressure difference; the magnitude of the pressure gradient indicates the severity of obstruction (Fig. 24–1).

A diastolic gradient across an atrioventricular valve implies mitral or tricuspid stenosis, whereas a systolic gradient across a semilunar valve denotes pulmonic or subaortic stenosis. All gradients depend on transvalvular flow. They can be artificially diminished by heart failure, anesthetic agents, hypovolemia (from diuretics), arrhythmias, or combinations of lesions that reduce transvalvular flow across the narrowed region (e.g., mitral stenosis with aortic stenosis; tricuspid regurgitation with pulmonic stenosis). Conversely, sympathetic stimulation can enhance a gradient by increased blood flow with inotropic stimulation.

A pressure gradient does not always indicate valvular stenosis. For example, when there is a large left-to-right shunt, a systolic gradient of between 5 and 20 mmHg may develop across the pulmonary valve. This gradient can be attributed to "relative" valvular stenosis, the physiologic obstruction caused by increased blood volume traversing a normal valve orifice.

PRESSURE RESISTANCE RELATIONSHIPS AND SHUNTING. Arterial pressures recorded during catheterization are proportional to the product of blood flow and vascular resistance. Normal right and left ventricular outputs are virtually identical. Because the pulmonary vascular resistance is only about 12 percent of the systemic resistance, the resultant mean pulmonary arterial and

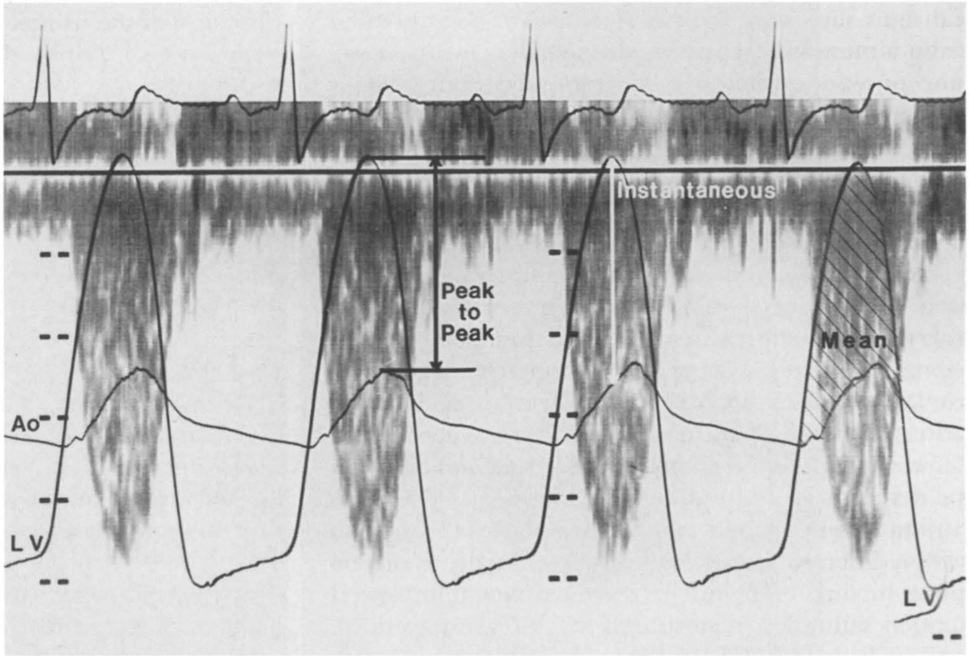


FIGURE 24–1

Pressure gradients: Simultaneous pressure recordings taken from the left ventricle *(LV)* and ascending aorta *(Ao)* from a dog with congenital subvalvular aortic stenosis. The methods of measuring systolic pressure gradients across a stenotic lesion are depicted as peak-to-peak, instantaneous, or mean pressure difference. Simultaneous, continuous-wave Doppler echocardiographic velocity spectra are demonstrated. Thus, outflow tract obstruction can be measured directly by cardiac catheterization or estimated using Doppler echocardiographic techniques (chapter 8). ECG trace appears above.

pulse pressures are much lower than those measured in the aorta.[7] This is also reflected in the increased wall thicknesses, and correspondingly, less distensible left atrial and ventricular chambers.

The obvious consequence of these pressure/resistance relationships is observed when a communication persists between systemic and pulmonary circulations. In this instance, blood shunts from the higher to the lower pressure system (i.e., from left to right). Patent ductus arteriosus and large septal defects commonly lead to significant left to right shunting with pulmonary overperfusion, unless there is concurrent tricuspid or pulmonary stenosis or elevated pulmonary vascular resistance. When resistance is abnormally high on the right side of the circulation, however, shunting will be minimal, bidirectional, or predominately right to left.

Cardiac catheterization will document the disparity in pressures in most cases of shunting; however, differences of peak systolic pressures between left and right sides of the circulation do not necessarily indicate the degree of shunting. Resistance to flow is another key factor. For example, with a large (unrestrictive) ventricular septal defect, both ventricles behave as a common chamber, and systolic pressures virtually equilibrate. Since blood flows across the path of least resistance, if the pulmonary resistance is normal, a tremendous left-to-right shunt can develop. The opposite situation is observed with severe pulmonary hypertension caused by Eisenmenger's physiology. In this case, the peak systolic pressures are approximately equal across the defect, but the lower systemic vascular resistance leads to a predominately right-to-left shunt. This type of shunt is often exacerbated by exercise owing to arteriolar vasodilation in skeletal muscle and increased sympathetic activity, which can promote dynamic muscular obstruction in the right ventricular outflow tract.

PULMONARY HYPERTENSION. Pulmonary artery pressure has an impact on clinical signs, prognosis, and management of patients with shunts. Estimation or calculation of vascular resistances is useful in these animals.[60a] We emphasize that measurement of pulmonary artery pressure alone does not accurately reflect the state of pulmonary vascular resistance.

Pulmonary hypertension (PH) may result from increases in flow through the lung, increased pulmonary vascular resistance, or both.[14] Pulmonary vascular resistance can be increased as a result of (1) left-sided heart failure (with elevated pulmonary wedge pressure), (2) left-sided valvular obstruction, or (3) anatomic narrowing of the pulmonary arterial system. Unless pulmonary and systemic blood flow are measured by thermodilution or indicator dilution techniques, the clinician may be uncertain whether pulmonary hypertension represents high flow, left-sided heart failure, or irreversible arteriolar change. This distinction may be critical to therapeutic decisions, as in the case of a ventricular septal defect in which PH due to high flow is an indication for repair or pulmonary artery banding, whereas PH due to arteriolar damage injury and increased resistance is a contraindication to surgery. Oximetry and evaluation of peripheral lung perfusion on the thoracic radiograph can also yield important information about vascular resistance.

VENTRICULAR DIASTOLIC PRESSURE. Elevated ventricular end-diastolic pressure is serious and may lead to clini-

cal signs such as tachypnea or ascites. This can result from a number of abnormalities: ventricular hypertrophy or endocardial fibrosis with increased diastolic ventricular stiffness; volume overloading as with left-to-right shunting or incompetent cardiac valves; ventricular failure; pericardial disease; or a combination of these problems.

OXIMETRY. Blood oxygen content (ml O_2/dl blood) is a product of the oxygen saturation and oxygen-carrying capacity (proportional to hemoglobin concentration). Oxygen saturation values, from left atrium to left ventricle, to ascending aorta to descending aorta, are normally within 1 to 2 percent of each other. However, differences of up to 5 percent saturation may be detected on the right side of the heart. The right atrium receives blood from a variety of sources, each with a different oxygen saturation, and there is incomplete mixing of blood in this chamber. The lowest oxygen saturation is measured at the coronary sinus, and we have found the cranial vena caval saturation to be higher than that of the azygos vein or caudal vena cava in samples obtained from anesthetized dogs breathing 33 percent oxygen. Although differences of greater than 5 percent saturation are suspicious for shunting, even these differences can be encountered within the right atrium of some dogs who do not have intracardiac shunting.

Catheterization of patients with intracardiac or extracardiac shunting may demonstrate oxygen "step-ups" or "step-downs." For example, a marked increase in oxygen saturation (or content) in the right ventricular outflow tract suggests a left-to-right–shunting ventricular septal defect or pulmonary insufficiency in a case of patent ductus arteriosus. Right-to-left shunting leads to desaturation of arterial blood, beginning at the level of the shunt. Formulas have been devised to estimate the degree of cardiac shunting (Qp:Qs), calculated from oxygen content and indicator dilution techniques (chapter 9). Surgical decisions based on shunt calculations should be interpreted with other information, including pulmonary artery pressure, pulmonary vascular resistance, results of thoracic radiography, and clinical signs.

LABORATORY TESTS

Hematologic tests are not an important part of the diagnostic workup. Serum biochemical tests may be abnormal when there is congestive heart failure or intercurrent organ disease (e.g., portosystemic shunting), but the complete blood count (CBC), biochemical profile, and urinalysis are typically normal. One exception is a higher-than-normal packed cell volume (PCV) in a neonate with right-to-left shunting. Polycythemia is often noted with tetralogy of Fallot, reversed patent ductus arteriosus, and complex cyanotic heart disease.[61] Arterial hypoxemia, hypocapnia, and metabolic acidosis may be detected in cases of right-to-left shunting.

LESIONS CAUSING VENTRICULAR OUTFLOW OBSTRUCTION

PULMONIC STENOSIS

Pulmonic stenosis (PS) is a common congenital heart defect in dogs (see Table 23–8) and is occasionally recognized in cats.[9, 22, 33, 45, 56, 62–67] Although obstruction to right ventricular outflow can develop in the infundibulum, in the subvalvular region, and above the pulmonic valve, dysplasia of the pulmonary valve is the most frequently observed defect in dogs. Subvalvular or valvular pulmonic stenoses are also recognized in animals with tetralogy of Fallot. Right ventricular outflow obstruction in the extreme form is represented as pulmonary artery atresia.

Pulmonic stenosis has a frequency of approximately 11 to 18 percent of congenital cardiac defects[5, 33, 34] and demonstrates a genetic basis in certain canine breeds (see Table 24–1). The etiology in cats is unknown. In beagle dogs, a polygenetic mode of transmission was responsible for abnormal development of pulmonary valve anlagen, leading to valve dysplasia.[68] These results are likely to be applicable to other affected breeds.

LESIONS

GROSS MORPHOLOGY. A spectrum of abnormalities was observed in pulmonary valve dysplasia of beagles, and graded thus[68]: grade 1—"slight thickening of pulmonary valve leaflets with little or no fusion or hypoplasia, producing minimal or no demonstrable pulmonary outflow obstruction," and grade 2—"moderate-to-severe thickening of pulmonary valve leaflets, usually with fusion, hypoplasia, or both, producing moderate-to-severe pulmonary outflow obstruction." Clinical cases of pulmonic stenosis (PS) usually represent a grade 2 lesion. We have observed similar findings in other breeds (Fig. 24–2). Many of these dogs also have fibrous thickening at the immediate base of the valves in addition to abnormal valve leaflets. Such thickenings may account for the preponderance of "subvalvular" PS in some surveys. Pulmonic stenosis of the dog more closely resembles atypical PS in children.[14]

Anomalous coronary artery development is present in some affected dogs, especially in English bulldogs and boxers. It is characterized by an anomalous left main coronary artery (originating from a single right

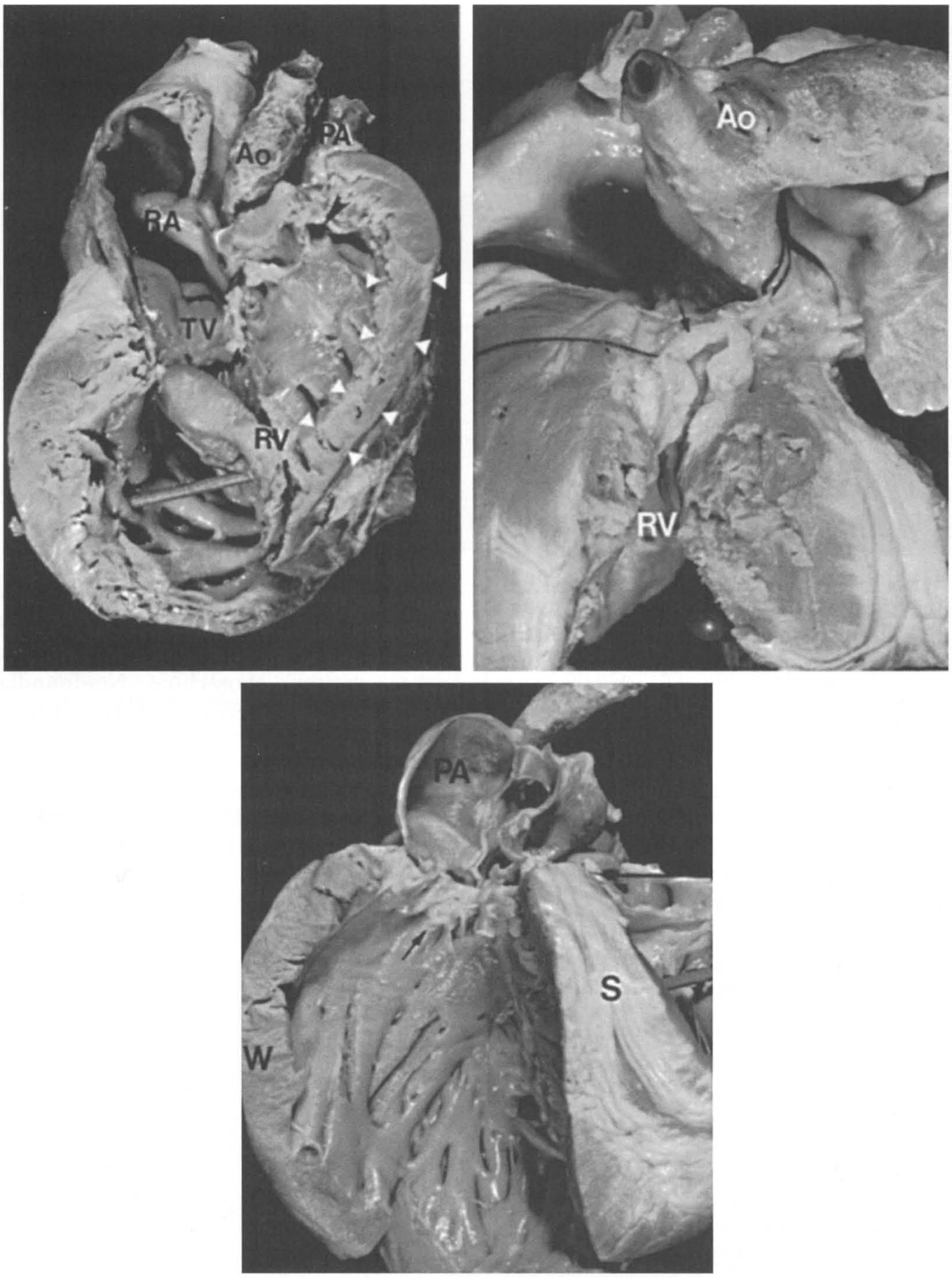


FIGURE 24–2

Pathology of congenital pulmonic stenosis. Hearts obtained from three dogs with pulmonic valve dysplasia show some of the variable features. *Upper right,* Dysplastic pulmonary valve viewed from above. The main pulmonary artery has been cut away to illustrate the thickened, partially fused pulmonary valve leaflets *(arrow).* The right ventricle *(RV)* and the aorta *(Ao)* are indicated. *Lower center,* Right ventricular enlargement with hypertrophy of the right ventricular wall *(W)* is evident in this dog with pulmonic valve dysplasia *(arrow).* The pulmonic valve leaflets are thickened and malformed, and the thickening extends to the base of each valve. The main pulmonary artery *(PA)* is dilated as a result of poststenotic dilation. The ventricular septum is noted *(S). Upper left,* Hypoplasia of the pulmonary valve *(arrow)* is evident in this specimen viewed from the ventral surface. There is marked hypertrophy of the right ventricle, papillary muscles, infundibulum *(white arrowheads),* and supraventricular crest between the tricuspid valve *(TV)* and the pulmonary valve *(upper arrow).* The right atrium *(RA),* aorta *(Ao),* and the main pulmonary artery *(PA)* are indicated.

(From Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 918, with permission.)

coronary artery), which encircles the stenotic right ventricular outlet and valve and probably contributes to the embryogenesis of the obstruction (Fig. 24–3).[45]

Other forms of PS have been described. Supravalvular stenosis is quite uncommon in animals. It is perhaps most often observed in giant schnauzers. Rarely, a true subvalvular partitioning of the right ventricular inlet and outlet is produced by fibromuscular or muscular bands, a condition that has been referred to as double-chambered right ventricle (Fig. 24–4).[14, 69]

Concurrent tricuspid valve malformation may be present, particularly in larger breeds. The distinction between mild dysplasia and secondary changes in the valve apparatus resulting from hypertrophy and valve thickening is not always clear.

HISTOLOGIC FEATURES. Thickening of the valve spongiosa and bands of fusiform cells present in a dense collagen network are observed.[68] These changes represent over-production of normal valve elements or a failure of conversion of the cushion-like embryonic valve primordia. Blood-filled spaces and endothelium-lined spaces are also found in one or more cusps of affected dogs.

PATHOPHYSIOLOGY

The pathophysiology of PS is summarized in Figure 24–5. Obstruction to right ventricular outflow causes an increase in ventricular systolic pressure (RVSP), leading to right ventricular hypertrophy (RVH), leftward septal deviation or flattening, and a systolic pressure gradient across the pulmonary valve. High-velocity and turbulent flow about the stenosis is associated with a systolic ejection murmur and poststenotic dilation of the main pulmonary artery (PA). Increasing stiffness of the right ventricle is responsible for the vigorous atrial contraction (*a* wave) that may be evident in the jugular venous furrow. Diminished right ventricular coronary blood flow has been documented in dogs with PS.[65] Critical stenosis limits cardiac output. If right atrial pressures become markedly elevated, right-sided congestive heart failure develops. Progressive right atrial enlargement probably results from various factors, including outflow obstruction, elevated ventricular diastolic pressure and diastolic dysfunction, secondary tricuspid regurgitation caused by high systolic pressure and geometric changes within the ventricle, and decreased cardiac output with compensatory retention of sodium and water.

CLINICAL FINDINGS

SIGNALMENT. Pulmonic stenosis is common in certain breeds, including the beagle, Samoyed, Chihuahua, English bulldog, miniature schnauzer, Labrador retriever, mastiff, chow-chow, Newfoundland, basset hound, and other terrier and spaniel breeds (see Tables 23–8; 24–1).[14a, 34]

CLINICAL SIGNS. Dogs with PS may be asymptomatic; develop signs related to low cardiac output, such as syncope and tiring; manifest right-sided congestive heart failure[56]; or develop hypoxemia from right-to-left shunting across an atrioventricular septal defect or patent foramen ovale.[59] Clinical signs are more likely in dogs older than 1 year.

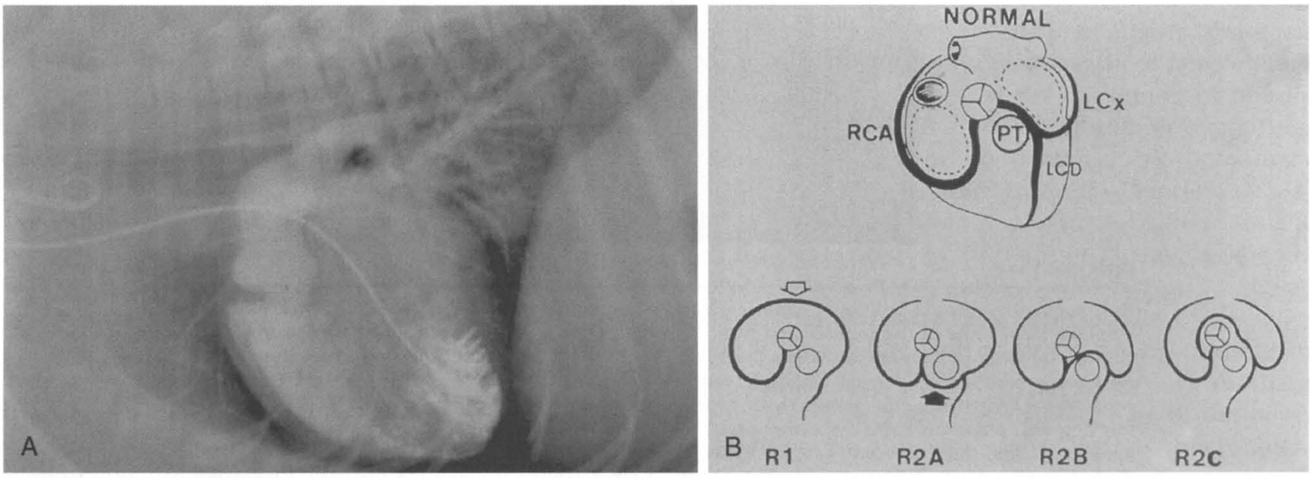


FIGURE 24–3

Pulmonic stenosis related to an anomalous coronary artery. (A) Right ventricular angiocardiogram from a dog demonstrates an asymmetric filling defect along the cranial aspect of the ventricular outlet. This corresponds to the location of the abnormal coronary vessel. (B) Comparison of normal origin versus anomalous single origin of the coronary arteries. (From Buchanan JW. Pulmonic stenosis caused by single coronary artery in dogs: Four cases (1965–1984). J Am Vet Med Assoc 196:115–120, 1990, with permission.)

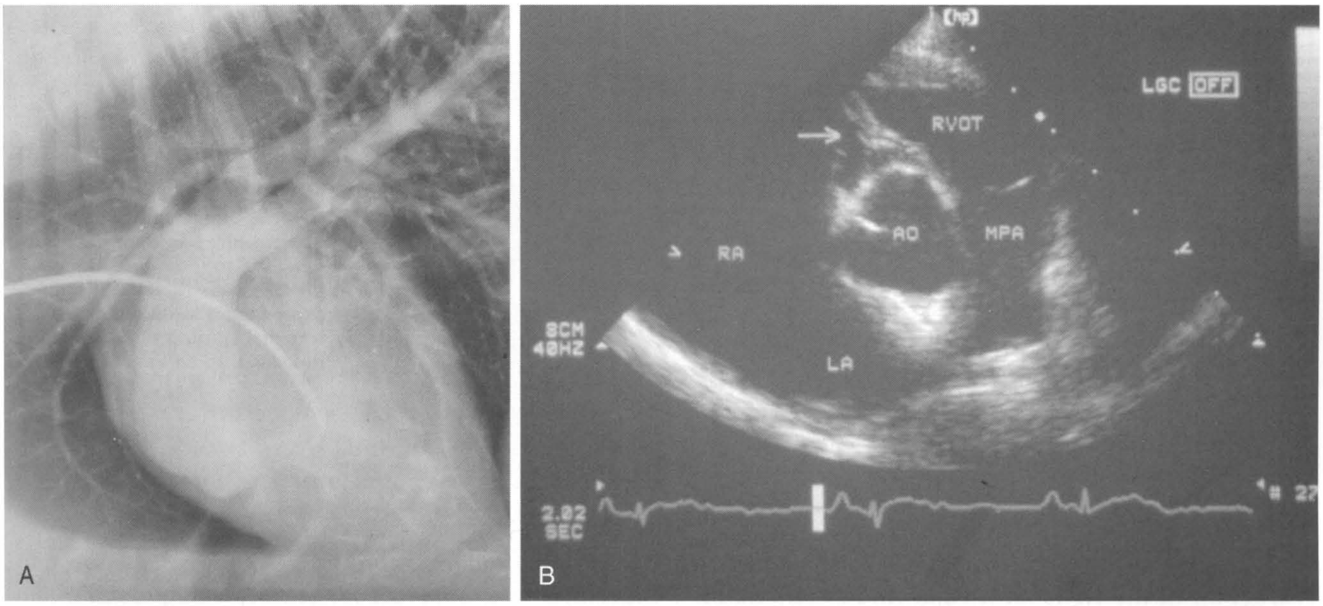


FIGURE 24–4

Double-chambered right ventricle. (A) Angiocardiogram from a dog showing irregular narrowing just proximal to the origin of the right ventricular outlet. The pulmonary valve is normal. (B) Echocardiogram demonstrating a ventricular obstruction *(arrow)* at the origin of the right ventricular outflow tract *(RVOT)*. The atrial septum is not visualized in this image. *RA*, right atrium; *LA*, left atrium; *AO*, aorta; *MPA*, main pulmonary artery.

PHYSICAL EXAMINATION. Findings may include a prominent jugular pulse; left basilar ejection murmur over the pulmonic valve that radiates to the left craniodorsal cardiac base; and palpable right ventricular hypertrophy (right-sided heave). It is not uncommon to auscultate a holosystolic murmur of tricuspid regurgitation over the right hemithorax.

ELECTROCARDIOGRAPHY. Right ventricular enlargement is often evident (Fig. 24–6; see also Figure 6–15). These ECG criteria are described in chapter 6.

RADIOGRAPHY. Right-sided cardiomegaly is usually present (Fig. 24–7; see also Figures 7–10, 7–12). Additional radiographic features include poststenotic dilation of the main pulmonary artery (Figs. 7–12; 24–7), variable dilation of the proximal left pulmonary artery, and pulmonary underperfusion.[36–40, 56]

CARDIAC CATHETERIZATION. Findings usually include a systolic pressure gradient across the obstruction, elevated right ventricular end-diastolic pressure, and an elevated right atrial *a* wave. General anesthesia can markedly depress the pressure gradient compared with the unanesthetized state.

Angiocardiography is especially useful for surgical cases, and usually delineates the valvular obstruction and secondary changes in the ventricle and pulmonary artery. Angiocardiographic abnormalities include narrowed valve orifice; dysplastic pulmonary valves; right

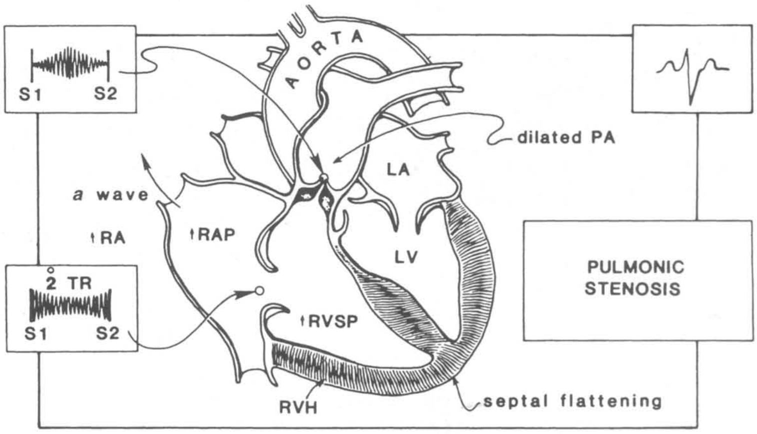


FIGURE 24–5

Pathophysiology and genesis of clinical findings in pulmonic stenosis (see text for details). (From Bonagura JD (ed). Cardiology, New York, Churchill Livingstone, 1987, with permission.)

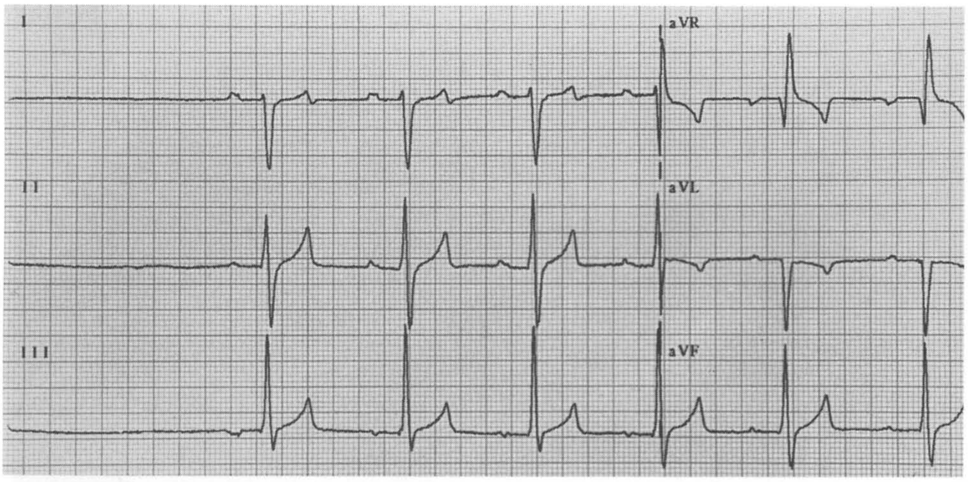


FIGURE 24–6

Electrocardiogram from a female basset hound with pulmonic stenosis. Right ventricular hypertrophy is evident, with axis deviation to the right (strongly positive leads III and aVR) and prominent S waves, indicating terminal craniodextrad activity, in leads I, II, and aVF.

ventricular hypertrophy; secondary dynamic muscular obstruction of the right ventricular infundibulum; enlargement of the right coronary artery; and poststenotic dilation of the pulmonary artery. Other coronary anomalies may be evident and influence the course of therapy as described later (see Figure 24–3). Angiographic features of pulmonic valve dysplasia consist of any combination of the following: narrowing at the immediate base of the valve sinuses, asymmetric valve sinuses, hypoplasia of the annulus or a valve sinus, thickening of individual valve leaflets producing a lucent filling defect, narrowing of the dye column with a central or asymmetric jet of contrast observed within a narrowed valve orifice, or systolic valve doming (indicating commissure fusion) (Fig. 24–8; see also Fig. 9–12*E*). Rarely, subvalvular, infundibular, or supravalvular stenoses occur.

ECHOCARDIOGRAPHY. Typical features include hypertrophy of the right ventricle, with increased prominence of the papillary muscles; secondary muscular narrowing of the right ventricular outflow tract in most

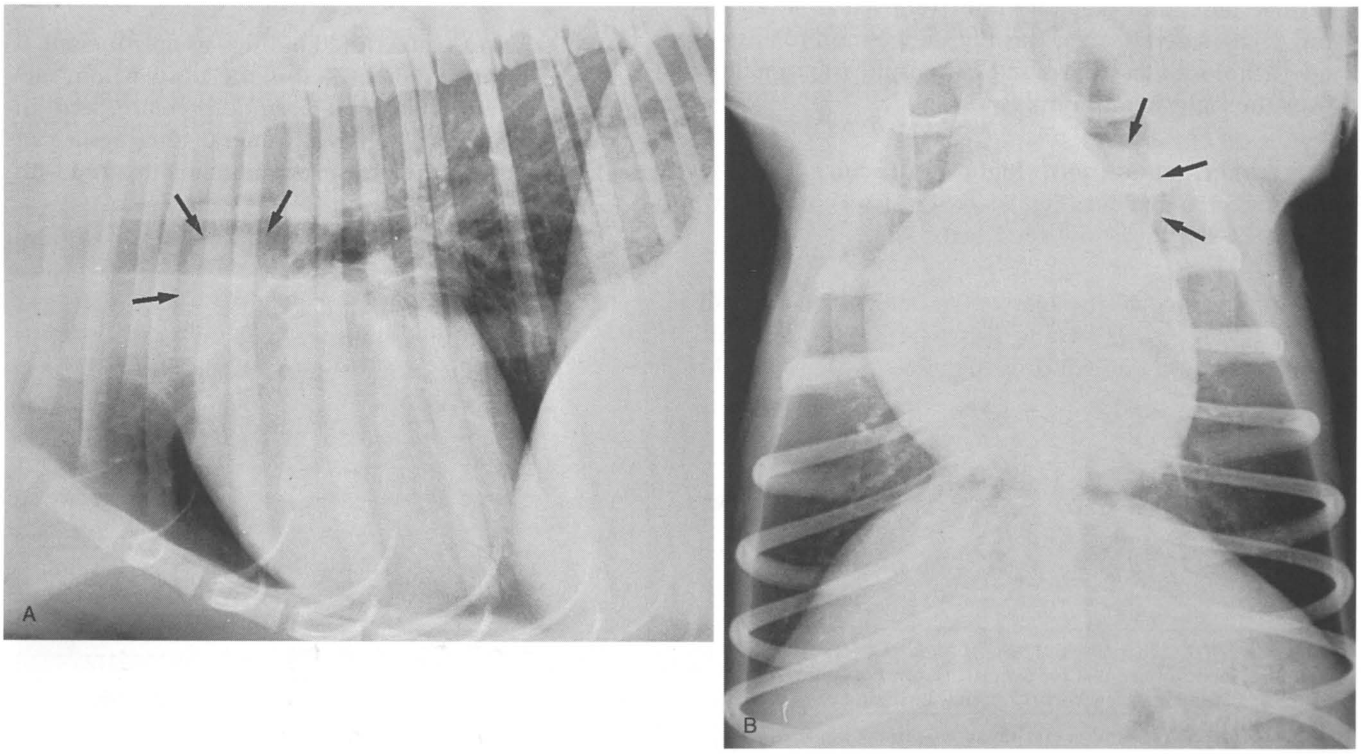


FIGURE 24–7

(A) and (B) Radiographs from a fox terrier with pulmonic stenosis. There is rounding of the right ventricular border and dilation of the main pulmonary artery on both views *(arrows)*. Pulmonary vascularity is reduced in the cranial lung lobe vessels.

cases; increased echogenicity of the pulmonary valve; and dilation of the main pulmonary artery (Fig. 24–9; see also Figure 8–20 and Color Plate 3). The pulmonary valve annulus may be hypoplastic or normal in size. Discrete subvalvular obstruction is uncommon. Doppler studies reveal increased blood velocity across the stenosis and turbulence in the pulmonary artery (see Figure 8–5*A*). Quantification of the outflow velocity can be used to estimate the right ventricular to pulmonary artery pressure gradient by the Bernoulli principle (chapter 8). A prominent tricuspid valve *a* wave may also be recorded.

GRADING OF LESION SEVERITY. This can be based on right ventricular systolic pressure and the pressure gradient.[58] Unlike the invasively measured gradient recorded in the anesthetized patient during catheterization, gradients estimated from Doppler studies can be obtained in awake or lightly sedated animals. Anesthesia significantly depresses pressure gradients; therefore, gradients measured by Doppler are generally preferable. As a general rule, Doppler gradients are 40 to 50 percent higher than the catheterization gradient measured in an individual dog.[58] The degree of stenosis can be graded arbitrarily by Doppler as:

- Mild (Doppler gradient up to 49 mmHg),
- Moderate (Doppler gradient of 50 to 100 mmHg), or
- Severe (Doppler gradient greater than 100 mmHg).

Some cardiologists use 80 mmHg as a delineation for "severe" stenosis. Other frequent findings at catheterization include elevated right ventricular end-diastolic pressure and a prominent atrial *a* wave.

CONCURRENT PULMONIC VALVE INSUFFICIENCY

Pulmonic valve insufficiency (PI) is an uncommon abnormality that has been observed in basset hounds, beagles, and other breeds.[70, 71] Abnormal development of valve leaflets or dilation of the pulmonary artery annulus has been observed in pups with congenital PI. The affected valve is usually mildly to moderately stenotic as well. This defect must not be confused with PDA, in which the murmur may be similar but the supporting electrocardiographic and radiographic findings are quite different.[36, 38, 50]

The combination of mild stenosis and moderate-to-severe valve insufficiency leads to right ventricular dilation. Heart failure can develop in severe PI induced experimentally in dogs; however, we have observed dogs that have lived for more than 5 years with substantial pulmonary insufficiency caused by valvular dysplasia. Differential considerations for pulmonic insufficiency include pulmonary hypertension, surgery, balloon catheter dilation, and stretching of the main pulmonary artery in dogs with PDA.

Clinical features include variable systolic (due to increased flow or concurrent stenosis) and diastolic murmurs. Enlargement of the main pulmonary artery and right ventricle may be evident on thoracic radiography. The ECG may show right ventricular enlargement. Angiography documents regurgitation in excess of that expected from the catheter and slow clearance of contrast from the dilated right ventricle (Fig. 24–10). Echocardiography may show diastolic fluttering of the tricuspid valve if the regurgitant jets strike the atrioventricular valve. Doppler studies document PI and can detect pulmonic stenosis or pulmonary hypertension when present (see Figure 8–4*A*). The diastolic, regurgitant PI jet will be of high velocity (>2.5 m/s) when there is pulmonary hypertension.

NATURAL HISTORY

The natural history depends on lesion severity. Dogs affected by mild and even moderate PS may live normally. Animals with moderate-to-severe stenosis may develop complications, including exertional syncope, cardiac arrhythmias, secondary tricuspid regurgitation, atrial fibrillation, congestive heart failure, and sudden death. Although systolic pressure gradients are not always predictive of clinical outcome, we have found a general correlation between pressure gradient and survival. When an ASD, patent foramen ovale, or VSD coexists with PS, the potential for right-to-left shunting, hypoxemia, and polycythemia exists.[59]

CLINICAL MANAGEMENT

Affected dogs should not be bred. If significant radiographic, ECG, and echocardiographic changes are evident, or if the patient has clinical signs of disease, the pressure gradient should be determined by Doppler echocardiography. The pressure gradient for which an operation should be recommended cannot be stated with certainty. However, the dog with a Doppler gradient of greater than 100 mmHg should be considered as a surgical or balloon valvuloplasty candidate.

If surgery is delayed in a dog with moderate-to-severe stenosis, the patient should be re-evaluated in 3 to 6 months. Over time, progressive infundibular hypertrophy can produce additional obstruction, and tricuspid regurgitation may worsen. Moreover, hypertrophy and fibrosis can lead to diastolic dysfunction that can induce elevated right atrial pressures and right-sided congestive heart failure (CHF) (Fig. 24–9*D*).

Surgery

A number of surgical procedures have been advocated for the treatment of severe PS.[45, 56, 62, 72–78] Valvulotomy, partial valvulectomy, patch-grafting over the

outflow tract, and conduits are most popular. Of critical concern is the nature of the subvalvular muscular hypertrophy (Fig. 24–8). If this is severe, simple valvulotomy may not be adequate to relieve obstruction. Moreover, valve dilation (Brock or balloon catheter dilation) can be initially successful but subsequently fail as a result of scarring. Thus, until more data are available concerning postoperative regression of muscular hypertrophy, we recommend that a patch-graft technique be employed in cases of valve dysplasia with significant subvalvular muscular hypertrophy.

Balloon Catheter Dilation (Valvuloplasty)

This technique is successful for some cases of valvular stenosis, especially when the valves are thin and

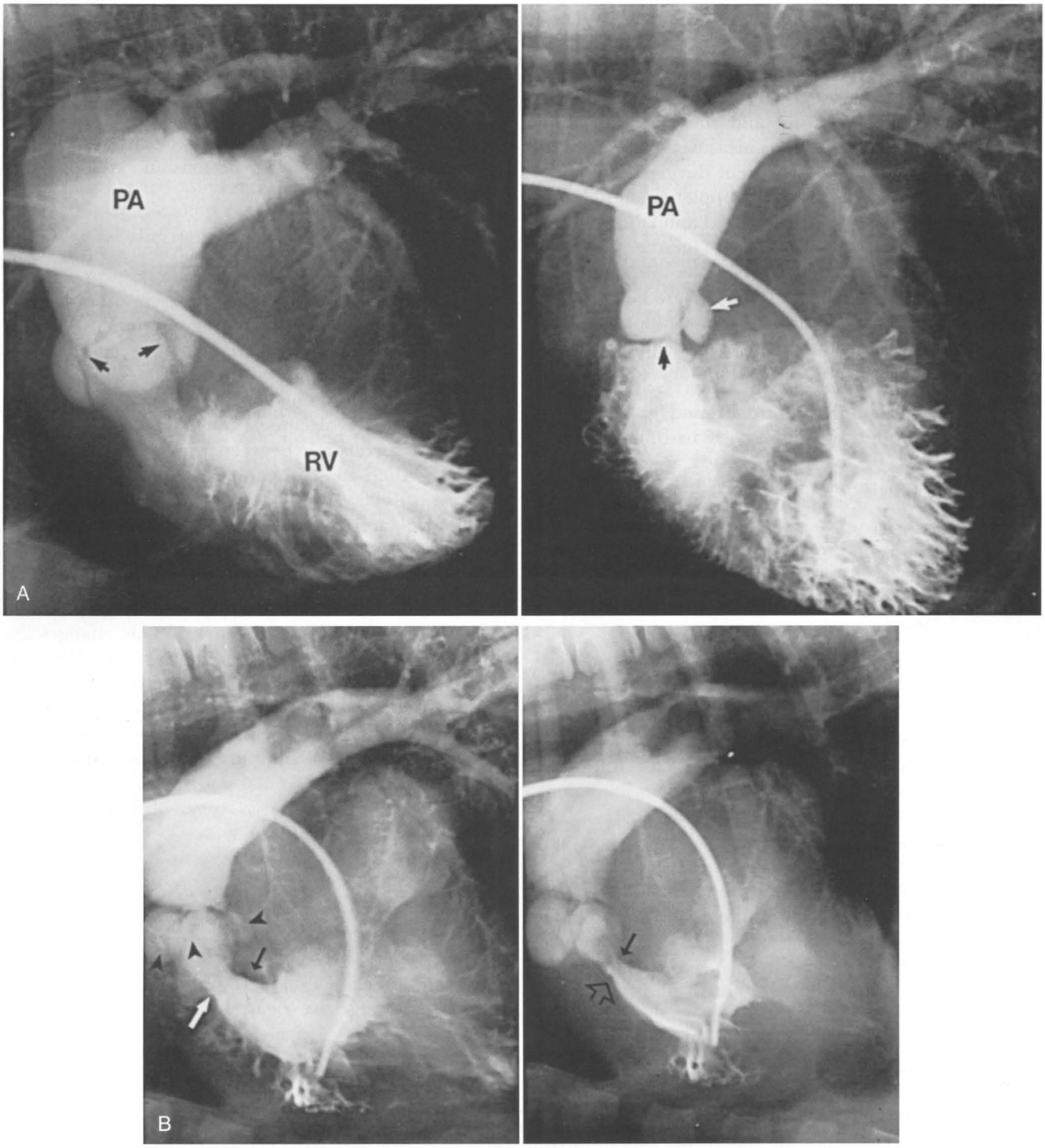


FIGURE 24–8. *See legend on opposite page*

TABLE 24–3
Medical Therapy of Congenital Heart Disease

Drug (Generic)	Proprietary Drug	Indications	Usual Dose	Dosing Interval
Digoxin	Lanoxin, Cardoxin	Congestive heart failure (CHF); atrial fibrillation	0.005 mg/kg	q 12 h
Furosemide	Lasix	CHF of any cause	1–4 mg/kg	q 8–12 h
Hydrochlorothiazide with spironolactone	Aldactazide (25 mg/25 mg)	CHF; particularly unresponsive edema or ascites	2–4 mg/kg of combined product	q 12–24 h; can alternate with furosemide
Enalapril*	Enacard, Vasotec	CHF due to left-to-right shunt; mitral regurgitation	0.25–0.5 mg/kg	q 12–24 h
Hydralazine*	Apresoline	CHF due to left-to-right shunt; mitral regurgitation	1–2 mg/kg	q 12 h
Propranolol	Inderal	Subaortic stenosis; atrial fibrillation	0.5–1 mg/kg	q 8 h
Atenolol	Tenormin	Subaortic stenosis; atrial fibrillation	0.25–1 mg/kg	q 12–24 h

*Beware of arterial vasodilator drugs in the setting of fixed left ventricular outflow obstruction.

fused and the annulus is not hypoplastic (Fig. 24–11).[58, 79–81] Since most cases of PS in the dog resemble atypical PS in children, the ultimate benefit of valvuloplasty in dogs remains to be determined. A single right coronary artery should be considered a contraindication to balloon valvuloplasty and may require placement of a conduit from right ventricle to pulmonary artery. Many dogs develop transient or persistent right bundle branch block subsequent to balloon catheter dilation (Fig. 24–11*B*).

Medical Therapy

When CHF or atrial fibrillation develops, the prognosis is poor. Medical stabilization with digitalis and diuretics (Table 24–3), should be accomplished prior to any surgical or catheter intervention.

AORTIC STENOSIS

Subvalvular aortic stenosis (subaortic stenosis, or SAS) is one of the most important congenital malformations of the canine heart (see Table 23–7) and continues to frustrate breeders of many larger breeds.[9, 18, 33, 82–88] Supravalvular stenosis is rare in dogs, although it has been described in the cat; and valvular aortic stenosis *per se* is quite uncommon.

Canine subaortic stenosis is probably the most commonly encountered congenital heart defect observed today in many veterinary hospitals, though it usually ranks second in frequency surveys. The current incidence has been estimated by Buchanan to represent between 22.1 and 34.6 percent of reported canine congenital heart disease.[34] In cats, aortic stenosis has been recognized only infrequently.[2, 8, 14a, 22, 89, 90]

It is clear that SAS and perhaps valvular aortic stenosis are propagated in breeds and families. The mode of inheritance is not that of a simple Mendelian transmission. Breeding studies in the Newfoundland established a genetic basis for the perpetuation of SAS.[9, 18] The mode of transmission is most compatible with an autosomal dominant trait with modifying genes or a polygenic mechanism.

LESIONS

Data derived from colony studies in the Newfoundland dog[9, 18, 34, 86, 87] are identical to the clinical features

FIGURE 24–8

Angiocardiograms obtained from dogs with pulmonic stenosis. (A) Angiocardiograms from two dogs with pulmonary valve dysplasia. *Right,* Following injection of contrast into the right ventricle, dye is funneled into a relatively small area in the region of the pulmonary valves *(lower arrow)* before it fills the main pulmonary artery *(PA).* Slight distortion of the pulmonary valve sinuses is evident *(upper arrow),* and there is marked thickening at the base of the valve sinuses. *Left,* thickening of the pulmonary valve cusp *(arrows)* is seen. Following the right ventricular injection, contrast funneled in a relatively narrow area of the pulmonary valve, surrounded the valve by filling the sinuses, and opacified the poststenotic dilation in the main pulmonary artery *(PA). RV,* right ventricle.

(B) Pulmonic stenosis in the dog; secondary muscular obstruction due to pulmonic valve dysplasia. *Left,* Following injection of contrast into the right ventricle, narrowing is evident just below the pulmonary valves due to hypertrophy of the ventricular infundibulum *(white arrow)* and the supraventricular crest *(black arrow).* The pulmonary valve is dysplastic and the valve sinuses unequal in size *(arrowheads).* Note that in the later systolic frame *(right),* there has been marked attenuation of the subvalvular region as a result of dynamic muscular obstruction *(arrows).*

(From Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 921, with permission.)

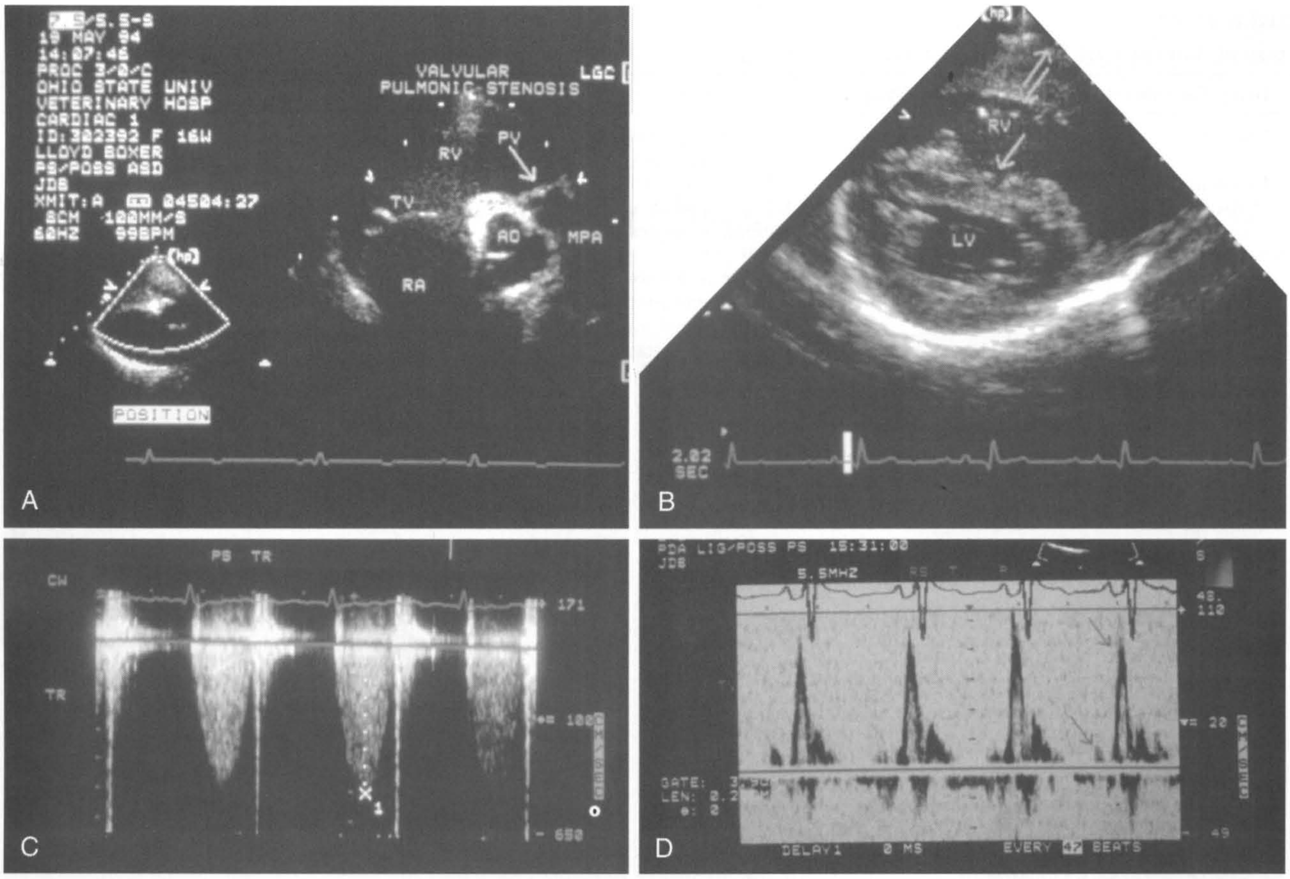


FIGURE 24–9

Echocardiograms obtained from dogs with pulmonic stenosis. (A) Image obtained from the short-axis view of the aorta demonstrates a thick (hyperechoic) pulmonary valve *(PV)*. The valve was partially fused and did not open fully during systole. *TV*, tricuspid valve; *RA*, right atrium; *RV*, right ventricle; *AO*, aorta; *MPA*, main pulmonary artery. (B) Short-axis image recorded in systole, which demonstrates marked right ventricular hypertrophy (*RVH* is encompassed by the double arrows) and flattening of the ventricular septum. These findings suggest systemic pressures in the right ventricular lumen. *RV*, right ventricle; *LV*, left ventricle.

(C) Continuous-wave Doppler echo recording demonstrating high-velocity tricuspid regurgitation from a bulldog with pulmonic stenosis, tricuspid incompetency, and congestive heart failure. The maximum regurgitant velocity of 5 m/sec is compatible with a right ventricular systolic pressure of at least 100 mmHg. Right ventricular to right atrial gradient = 4×5^2, as estimated by the modified Bernoulli equation [pressure gradient (mmHg) = $4 \times$ peak velocity $(m/s)^2$]. (D) Severe diastolic dysfunction in a 5-year-old West Highland white terrier with congenital pulmonic stenosis. Pulsed-wave Doppler echo recording: Early diastolic filling velocity *(lower arrow)* is virtually absent. A high-velocity atrial contribution (A wave, *upper arrow*) is evident. This waveform would correspond to a giant *a* wave in the jugular pulse or in the atrial pressure tracing. Simultaneous ECG is recorded above.

observed in other breeds with fixed anatomic SAS. The subvalvular obstruction may not necessarily be present at birth, but instead develops during the first 3 to 8 weeks of life. This progression has significance relative to the identification of cardiac murmurs in pups of breeds known to be at risk for SAS. The condition is known to recur in children following "successful" operation and the lesion may be progressive in some dogs.[35a] It is not uncommon to identify increased gradients in rapidly growing giant breed dogs affected with SAS.

GROSS MORPHOLOGY. Subaortic stenosis in Newfoundland dogs has been graded in postmortem studies as follows[18]: grade 1—the mildest form, consisting of "small, whitish, slightly raised nodules on the endocardial surface of the ventricular septum immediately below the aortic valve"; grade 2—a "narrow ridge of whitish, thickened endocardium" extending partially about the left ventricular outflow tract; grade 3—the most severe form, "a fibrous band, ridge, or collar completely encircling the left ventricular outflow tract just below the aortic valve" (Fig. 24–12). This ring is raised above the endocardium and extends to and may involve the cranioventral leaflet of the mitral valve and the base of the aortic valves. Auscultation and cardiac catheterization of dogs with grade 1 lesions failed to detect the postmortem lesion reliably, whereas grade 2

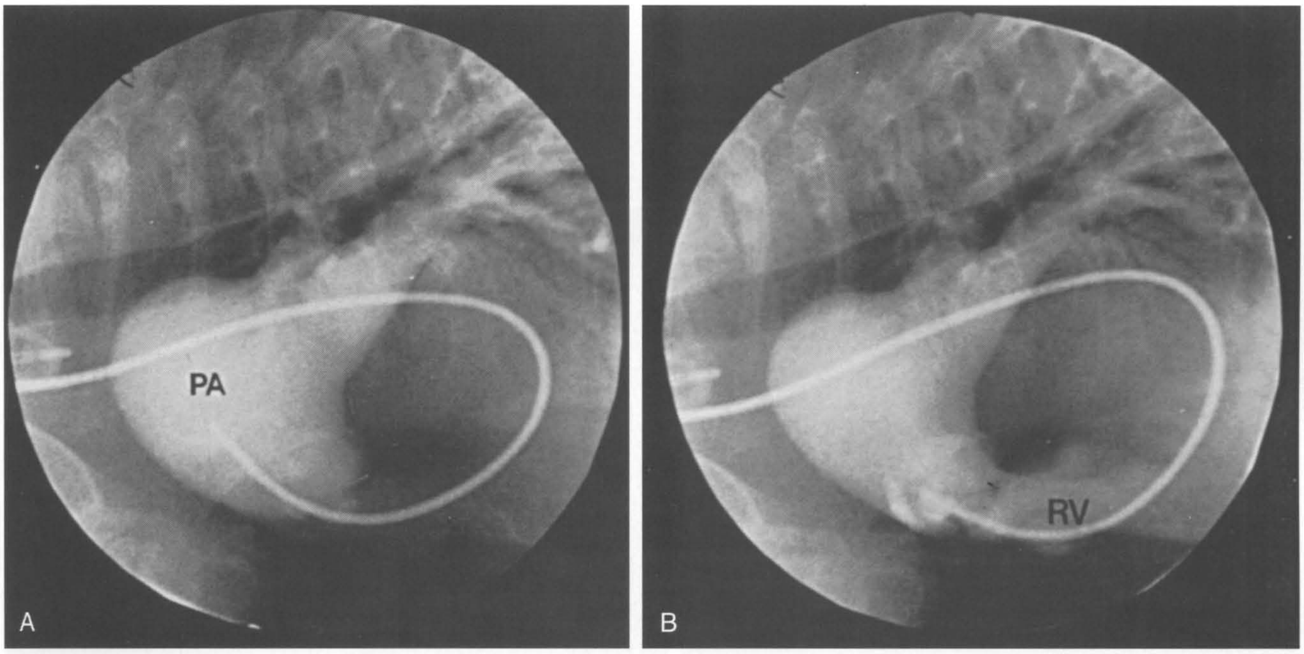


FIGURE 24–10

Pulmonic insufficiency in a basset hound with congenital pulmonary valve dysplasia (A) and (B). The contrast injection in the dilated main pulmonary artery results in marked opacification of the right ventricle. (From Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 923, with permission.)

lesions often were associated with soft cardiac murmurs and only minimal systolic pressure gradients. The clinical implication of these findings is clear: although genetic coding for SAS may be carried by a dog, clinical detection may be difficult to impossible in mild cases, and genetic counseling may be fraught with error. Associated necropsy findings include concentric left ventricular hypertrophy and myocardial fibrosis, left atrial hypertrophy, and aortic arch abnormalities. It is not uncommon to observe concurrent mitral valve malformations in dogs with SAS.[91] Dynamic obstruction also may be encountered.[92]

Focal areas of myocardial infarction and fibrosis have been observed in conjunction with intramural

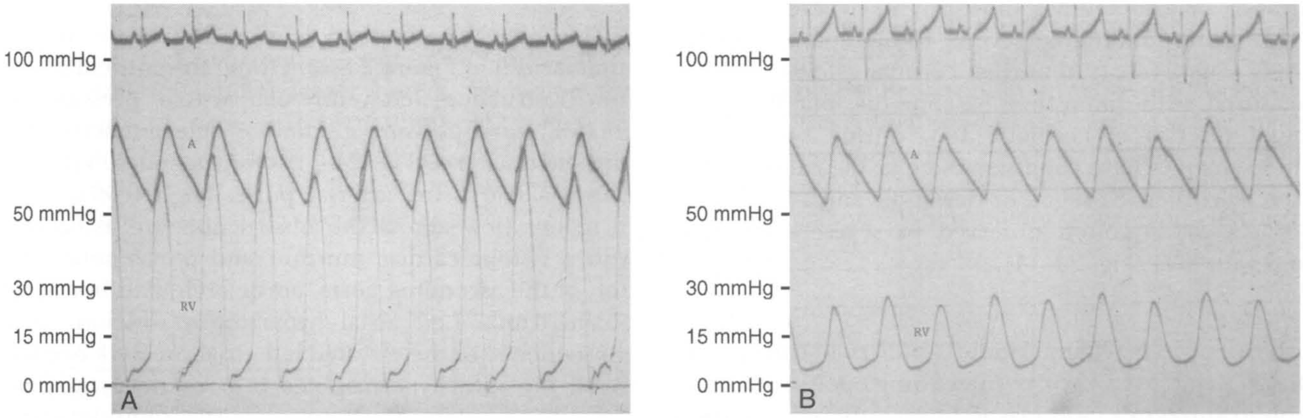


FIGURE 24–11

Right ventricular pressure before (A) and after (B) balloon catheter dilation of a stenotic pulmonary valve. (A) The right ventricular *(RV)* systolic pressure approaches systemic arterial pressure *(A)*, indicating severe stenosis. There is also elevated end-diastolic right ventricular pressure indicating increased diastolic stiffness or incipient ventricular failure. (B) Following balloon catheter dilation, the right ventricular *(RV)* systolic pressure markedly decreases relative to the systemic pressure *(A)*. Right bundle branch block has developed *(B)* as a consequence of the sudden increase in intraluminal right ventricular pressure that occurs during balloon inflation. Also note the depressant effects of anesthesia on the systemic pressures in both tracings. This effect must be considered in comparing pressure gradients obtained under anesthesia relative to those recorded in awake animals.

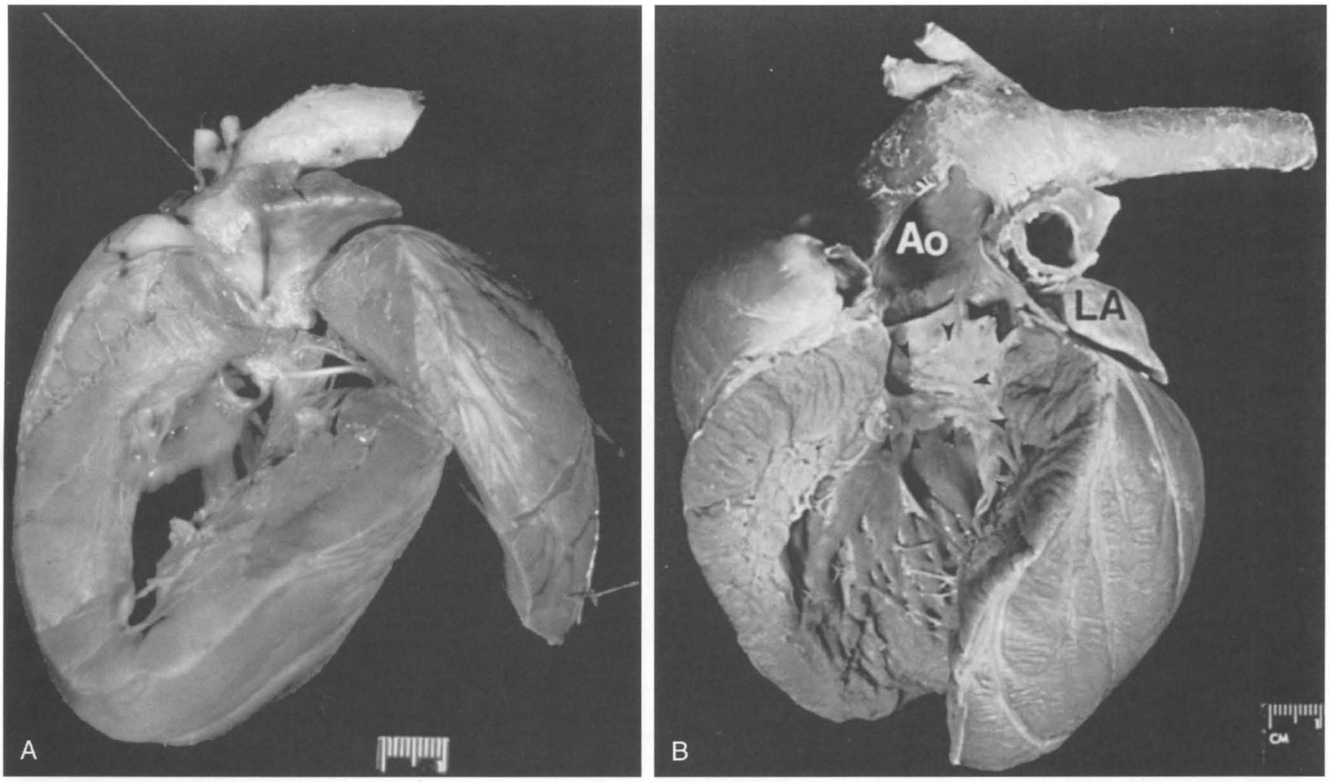


FIGURE 24–12

Pathology of subvalvular aortic stenosis in the dog. (A) Severe congenital subaortic stenosis in a bull terrier that died of congestive heart failure. The opened left ventricle is markedly hypertrophied. A fibrous subaortic ring, through which the left ventricular stroke volume must pass, is evident in this dissection. (B) Specimen from a dog with subaortic stenosis. An extensive subaortic valvular fibrous ring *(arrowheads)* extends from the cranioventral mitral leaflet to the base of the aortic valve cusps. There is poststenotic dilation of the ascending aorta *(Ao)*. The left auricle *(LA)* is indicated. There is marked left ventricular hypertrophy. (From Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 924, with permission.)

coronary arterial changes. Two-dimensional echocardiography may sometimes show bright, hyperechoic regions corresponding to severe, focal replacement fibrosis (Fig. 24–13). Abnormal coronary flow has been measured, with diminished baseline diastolic flow and actual reversal of coronary flow during systole.[82, 87] These changes have been suggested as the cause of the exercise-related ST-segment deviation and ventricular extrasystoles so often observed in severely affected dogs with SAS (Fig. 24–14).

HISTOLOGIC FEATURES. The stenotic ring consists of loosely arranged reticular fibers, mucopolysaccharide ground substance, and elastic fibers. Discrete bundles of collagen and even cartilage are found in advanced lesions.[18] Coronary circulation in dogs with SAS is abnormal.[82, 87] Extensive intramural coronary artery pathology occurs, including intimal proliferation of connective tissue and smooth muscle, and medial degeneration. These changes presumably result secondary to high ventricular wall tension.

PATHOPHYSIOLOGY

The clinical pathophysiology of SAS in the dog is summarized in Figure 24–15. Owing to ventricular outflow obstruction, left ventricular systolic pressure increases, and a pressure gradient is detected across the outflow tract (see Fig. 24–1). Obstruction to ejection causes a late rising arterial pulse. High velocity and turbulent flow across the obstruction are associated with a systolic cardiac murmur and poststenotic dilation of the ascending aorta, aortic arch, and brachycephalic trunk. Left atrial hypertrophy develops as a consequence of the elevated left atrial pressure needed to fill the stiff, hypertrophied left ventricle. In some cases, a to-and-fro murmur of aortic stenosis/aortic regurgitation is evident (Fig. 24–16). Aortic regurgitation can be related to involvement of the valve leaflets with the fibrous ring, jet lesions leading to thickening of the valve leaflets, dilation of the ascending aorta, or bacterial endocarditis. Left ventricular hypertrophy and myocardial ischemia are responsible for changes in the QRS complex and ST-T segment (Fig. 24–14).

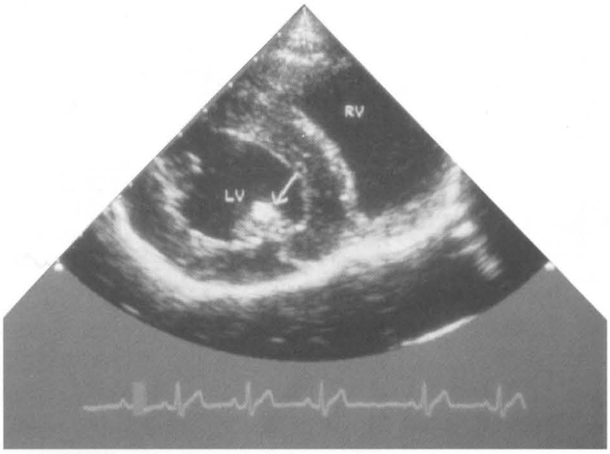


FIGURE 24–13

Myocardial fibrosis in congenital subvalvular aortic stenosis. Short-axis, two-dimensional echocardiogram at the level of the papillary muscles, demonstrating a focal hyperechoic zone of tissue *(arrow)* at the tip of the cranioventral papillary muscle. This change is usually caused by extensive loss of myocardium with replacement by fibrosis. *RV*, right ventricle; *LV*, left ventricle.

Critical SAS can lead to left-sided congestive heart failure from myocardial failure, increased ventricular stiffness, mitral regurgitation, atrial fibrillation, or a combination of these factors. More often, exertional syncope or sudden death is reported. Although the cause of these is undetermined, likely mechanisms include the development of myocardial ischemia and malignant ventricular arrhythmias. In addition, severe hypotension might result from exercise-induced increases in left ventricular pressure, activation of ventricular mechanoreceptors, and inappropriate bradycardia or vasodilation.[14]

CLINICAL FINDINGS

SIGNALMENT. Congenital SAS is most common in North America among larger breeds, including the Newfoundland, boxer, German shepherd, golden retriever, and bull terrier (see Tables 23–7; 24–1). Other large breeds, such as the Rottweiler, Samoyed, and Great Dane, also may be overrepresented.

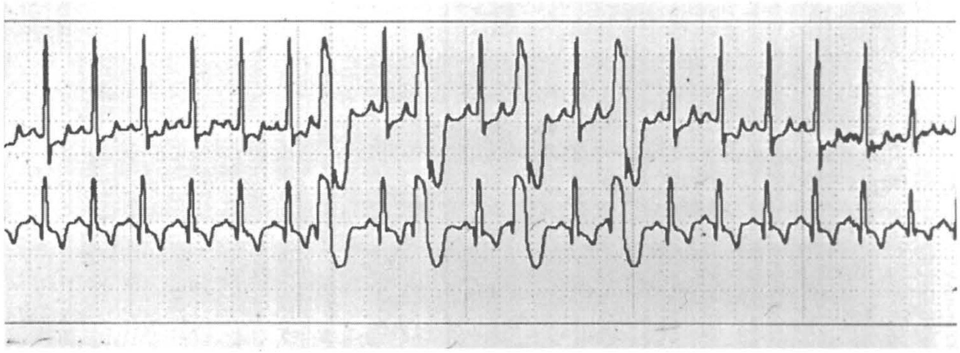
CLINICAL SIGNS. In pups with mild SAS, clinical signs are minimal.[4] Affected dogs are asymptomatic and have a soft-to-moderately intense ejection murmur that can easily be confused with a functional murmur, though it is most intense caudoventral to the location of most functional murmurs. Murmurs in dogs with mild cases of SAS, or in dogs with dynamic outflow tract obstruction, are best detected after a brief period of exercise.[92] More severely affected dogs may have with exertional tiring, rear limb weakness, syncope, or left-sided congestive heart failure. Sudden death, without premonitory signs, is common.

PHYSICAL EXAMINATION. Recognition of severe SAS is not difficult. The ventricular outflow obstruction generates an ejection murmur of variable intensity, and in some cases there is a soft, diastolic murmur secondary to incompetency of the aortic valve.[93] The murmur is most intense in the subaortic region (about the 4th intercostal space) and tends to radiate down the apex, up the carotid arteries, and even to the calvarium. Frequently, the systolic murmur is equally loud at the right cardiac base, presumably from radiation into the ascending aorta or from true valvular AS. As previously mentioned, SAS probably develops in the postnatal period; thus, the murmur may become increasingly prominent during the first months of life. We have noted an increasing number of dogs with both SAS and mitral regurgitation, but these murmurs can be somewhat similar in timing and point of maximal intensity and therefore can be difficult to distinguish. Other abnormalities can include an arterial pulse that is hypokinetic and tardy and a left ventricular apical impulse that is prominent from ventricular hypertrophy.

RADIOGRAPHY. The heart may be normal or indicate left ventricular and left atrial enlargement (Fig. 24–17). Poststenotic dilation of the aorta may result in widening of the mediastinum on the ventrodorsal view or loss of the cranial waist of the cardiac silhouette on the lateral view (see Fig. 7–14). Pulmonary circulation is normal unless pulmonary edema and venous congestion are present. When moderate-to-severe left atrial

FIGURE 24–14

Ambulatory electrocardiogram recorded from a dog with congenital subaortic stenosis demonstrating ST-segment depression (especially evident in the upper trace) and ventricular extrasystoles (characterized by wide, bizarre QRS-T complexes) in a dog with aortic stenosis (simultaneous thoracic leads).



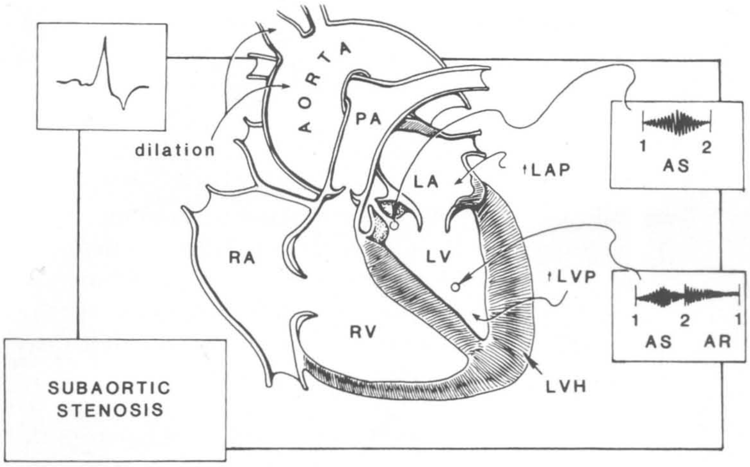


FIGURE 24–15

Pathophysiology and genesis of clinical signs in congenital subaortic stenosis. See text for details. (From Bonagura JD (ed). Cardiology. New York, Churchill Livingstone, 1987, with permission.)

enlargement is present, intercurrent mitral regurgitation should be suspected.

ECHOCARDIOGRAPHY. Echocardiographic imaging demonstrates left ventricular hypertrophy, a subvalvular fibrous ring that can involve the mitral valve, and post-stenotic dilation of the aorta (see Figs. 8–19; 24–12, 24–18, 24–19).[53, 54, 94–96] Doppler studies from the subxiphoid (subcostal) position are generally most accurate for quantifying increased velocity flow with turbulence beyond the stenosis (Fig. 24–20; see also Figs. 8–4; 24–16).[53] Doppler studies from the suprasternal notch and left apex can also be used to record the high-velocity systolic jet, and they may detect aortic regurgitation that is often inaudible during clinical examination (see also Color Plate 3). The left ventricular-to-aortic systolic gradient can be estimated (in mmHg) from the peak left ventricular outflow velocity (m/s) using the modified Bernoulli equation, $\Delta P = 4V^2$, where ΔP = pressure gradient and V = peak velocity (see Figs. 8–4; 24–1).[54] In mild cases of SAS, subtle changes in the velocity spectra are detected. These include resting maximal velocities of between 1.7 and 2.2 m/sec, associated with spectral dispersion, and mild aortic regurgitation. In advanced cases of SAS, changes in velocity spectra are dramatic, and maximal Doppler gradients of greater than 100 to 125 mmHg are considered severe. Mitral regurgitation may also be detected when there is concurrent mitral valve dysplasia, involvement of the septal mitral valve leaflet in the subaortic ridge, or geometric changes in the hypertrophied left ventricle. The mitral inflow E wave to A wave ratio may be reversed, indicating ventricular diastolic dysfunction, most likely caused by left ventricular hypertrophy or myocardial ischemia.[54]

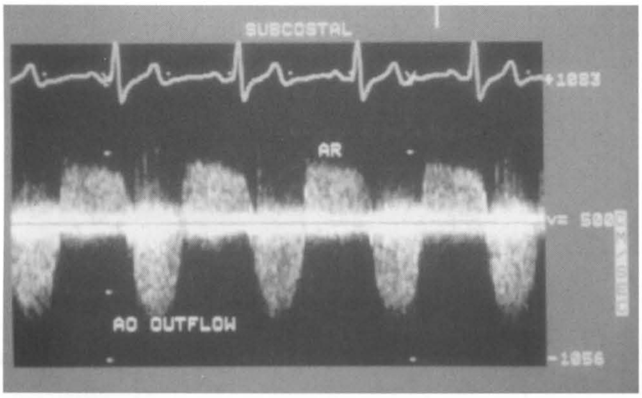


FIGURE 24–16

Continuous-wave Doppler echo recording from a dog with severe congenital subvalvular aortic stenosis and aortic regurgitation. Because a subcostal position was used, the systolic signal is negative and the diastolic, regurgitant signal is positive *(AR)*. Calibration dots are 5 m/sec; 1 second. Estimated peak pressure gradient exceeds 160 mmHg.

Fixed obstruction in the left ventricular outflow tract may be complicated by dynamic obstruction related to an abnormal mitral valve and outflow tract morphology (Fig. 24–21). Systolic anterior motion of the mitral valve may be recognized on M-mode studies in cases of dynamic outflow tract obstruction. Some dogs, notably golden retrievers, exhibit isolated, dynamic outflow tract obstruction.[88, 92] Cardiac murmurs or outflow tract pressure gradients may not be evident in affected dogs, unless provoked by exercise, infusions of catecholamines, or prior extrasystoles.

ELECTROCARDIOGRAPHY. The ECG is often normal or may indicate left ventricular hypertrophy in advanced cases.[4, 88, 97] Either left axis deviation or increased R-wave amplitude in lead II with a normal frontal axis can be observed. Widening of the QRS is not uncommon. ST-T segment depression (Fig. 24–14) is compatible with myocardial ischemia or left ventricular hypertrophy. Ischemia should be strongly suspected when exercise precipitates even greater ST-T change or ventricular arrhythmias. Holter (24-hour ECG) monitor studies often demonstrate exercise-induced ischemia or ventricular extrasystoles (Fig. 24–14). These changes are often, but not always, related to the severity of disease.

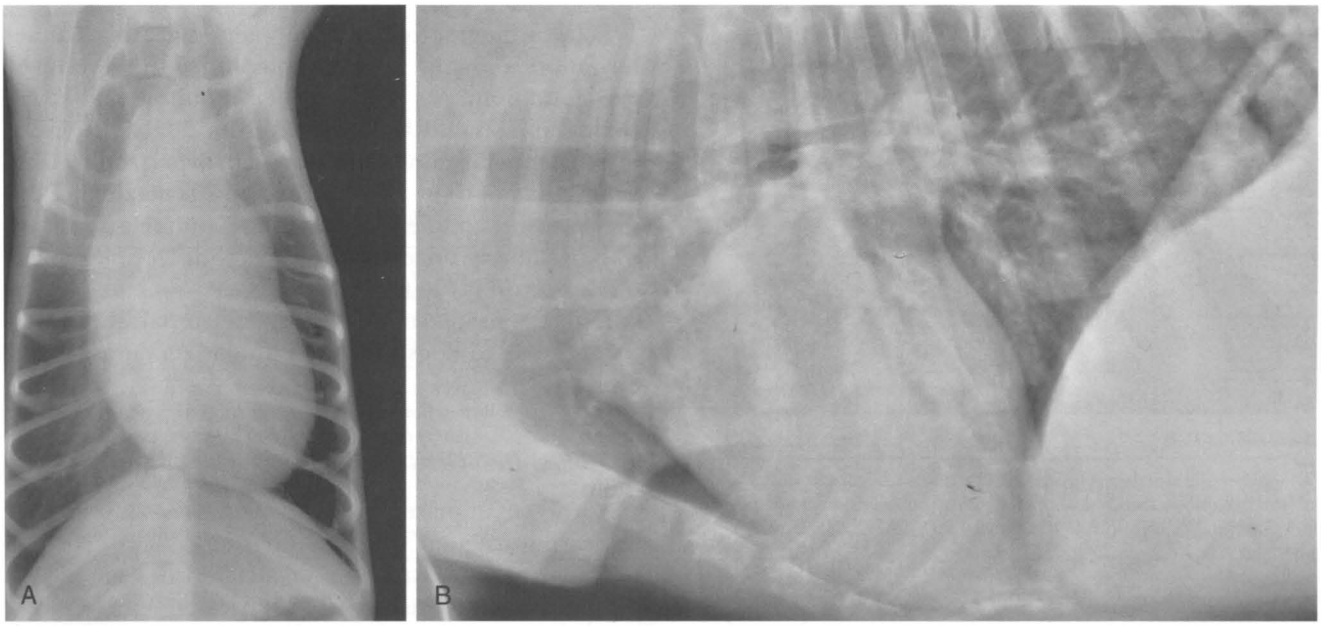


FIGURE 24–17

Radiographs obtained from two dogs with clinically significant congenital aortic stenosis. (A) Dorsoventral view of a dog with supravalvular aortic stenosis and aortic regurgitation. Left ventricular and left atrial enlargement, as well as dilation of the ascending aorta and aortic arch, are evident. Pulmonary venous enlargement is present. (B) Right lateral view of a dog with subaortic stenosis, secondary mitral regurgitation, and left-sided congestive heart failure. Widening of the cranioventral mediastinum related to poststenotic dilatation is evident. Left atrial dilatation in aortic stenosis usually stems from ventricular diastolic or systolic failure, mitral regurgitation, mitral stenosis, a concurrent left-to-right shunt, or atrial fibrillation. Progressive left atrial dilation often precedes the development of congestive heart failure.

CARDIAC CATHETERIZATION. Findings include a systolic pressure gradient across the obstruction and, generally, an elevation of ventricular diastolic pressure (Fig. 24–21; see also Figs. 24–1, 24–20). The pressure gradient in an individual dog is depressed by general anesthesia to approximately 40 to 50 percent of that measured in the unanesthetized state. Whereas Doppler and catheterization gradients are similar when recorded in the anesthetized dog (Fig. 24–20), the Doppler measured gradient will be greatest and most representative because it can be recorded in the unanesthetized state. This is the method we use to assess severity of a fixed obstruction. Maximal Doppler gradients of greater than 100 to 125 mmHg are considered severe.

The left ventriculogram outlines a relatively small ventricular cavity and illustrates the subvalvular obstruction, poststenotic dilation, and other intercurrent problems like mitral regurgitation (Fig. 24–22; see also Fig. 9–12*D*). The obstructive lesion is most evident in

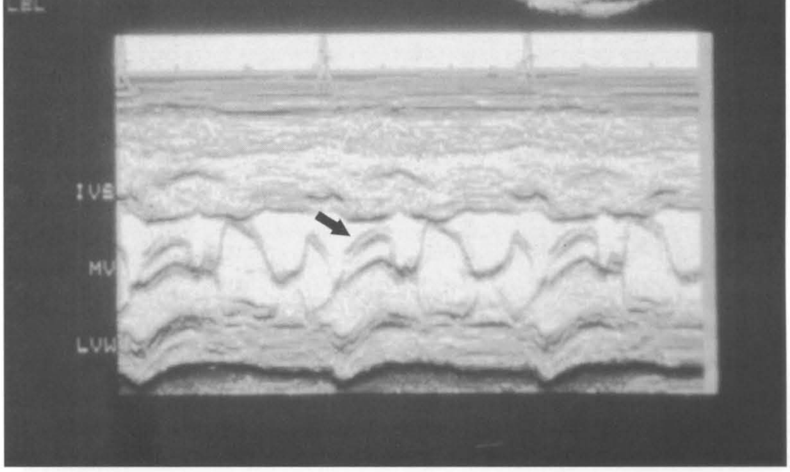


FIGURE 24–18

M-mode echo recording at the ventricular level of a dog with congenital subaortic stenosis. Hypertrophy of the ventricular septum *(IVS)* and left ventricular wall *(LVW)*, with systolic anterior motion of the mitral valve *(arrow)* are evident. The latter finding is compatible with a dynamic component of obstruction (see text for details).

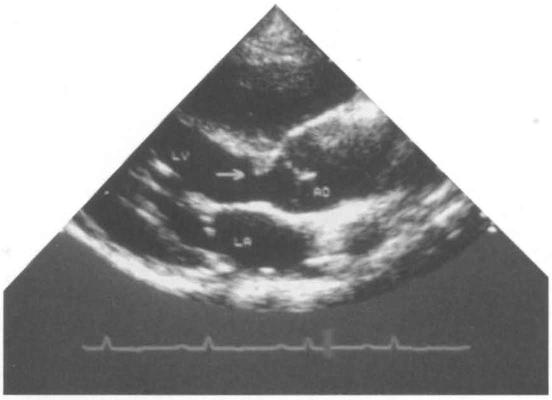


FIGURE 24–19

Two-dimensional echocardiogram of a dog with congenital subaortic stenosis demonstrates a discrete subvalvular ridge *(arrow)* and poststenotic dilation of the aorta *(AO)*. *LA*, left atrium; *LV*, left ventricle.

the ventral aspect of the outflow tract viewed on the lateral projection. A supravalvular aortic injection will rule out aortic insufficiency. The left coronary artery and its major extramural branches are often noted to be prominent, likely in response to increased oxygen demand.

NATURAL HISTORY

Severe SAS is a discouraging condition, since most dogs either die suddenly or develop congestive heart failure. Clinical examination in an asymptomatic dog cannot reliably predict the severity of the stenosis, though a long, loud, late-peaking ejection murmur and attenuated pulses suggest significant SAS. Mitral regurgitation, mitral stenosis, aortic regurgitation, aortic valve endocarditis, and atrial fibrillation cause additional complicating factors increasing morbidity and mortality. Medical therapy of CHF, endocarditis, or atrial fibrillation may be beneficial in some dogs. Congestive heart failure is particularly likely in dogs with intercurrent mitral valve malformation or severe aortic regurgitation.

Echocardiography (with Doppler) or cardiac catheterization is usually required to confirm the severity of the condition. An ECG, Holter monitor, and chest radiograph should be obtained from dogs with severe SAS. Dogs with minimal ventricular hypertrophy, mild ventricular outflow obstruction, and a maximal Doppler pressure gradient of less than 75 mmHg are likely to be relatively normal pets. Dogs with Doppler gradients exceeding 100 to 125 mmHg are prone to develop complications or sudden death. Bacterial endocarditis[98] is a risk to dogs with even mild-to-moderate gradients.

AORTIC REGURGITATION

Aortic regurgitation (AR) is being recognized with increasing frequency as a complication or concurrent problem of subvalvular or valvular aortic stenosis, as well as other defects such as ventricular septal defects (discussed later).[43, 99] Isolated congenital AR is rare. Aortic regurgitation may also develop as a complication of balloon catheter dilation or bacterial endocarditis, and with tetralogy of Fallot.

A diastolic murmur, heard best over the left hemithorax, is typical of moderate-to-severe AR. The diagnosis is supported by palpation of a hyperkinetic arterial pulse. More often, AR is inaudible but can be documented by angiocardiography or Doppler echocardiography (Fig. 24–16). Fine diastolic flutter of the mitral valve may be evident on M-mode echo recordings as the regurgitant jet of aortic insufficiency strikes the cranioventral mitral valve leaflet (see Fig. 8–12*D*).

CLINICAL MANAGEMENT

Dogs with mild-to-moderate SAS, as determined by detailed investigation, are treated normally but should not be used for breeding. Prophylaxis for bacterial endocarditis is prudent in appropriate circumstances. Dogs with moderate-to-severe SAS should have restricted exercise.

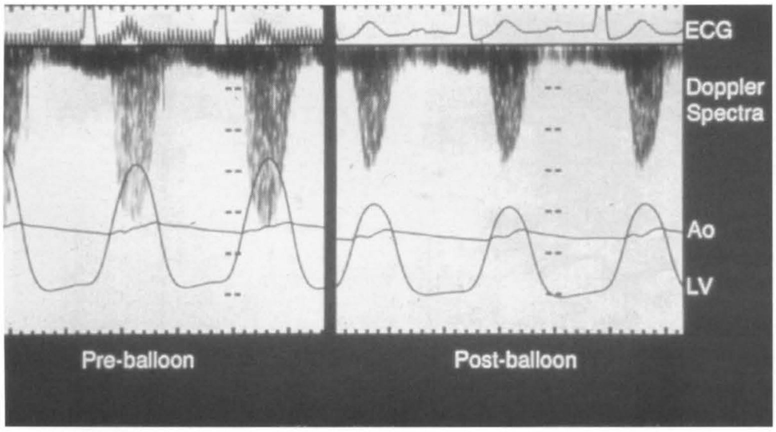


FIGURE 24–20

Catheterization and Doppler demonstration of pressure gradients in subvalvular aortic stenosis (also see Figure 24–1). Simultaneous pressure and continuous-wave Doppler studies obtained from a dog before and after catheter balloon dilation of the subvalvular ridge. Note the reduction in the pressure gradient and intercurrent decrease in peak aortic flow velocity following the intervention.

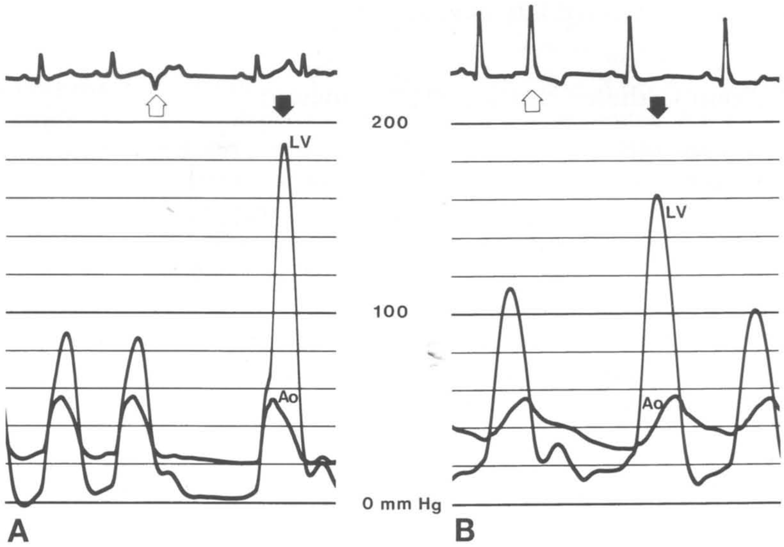


FIGURE 24–21

Simultaneous left ventricular *(LV)* and aortic *(Ao)* pressure tracings from two dogs with dynamic (A) and fixed (B) LV outflow tract obstructions. With dynamic obstruction (A), the LV and Ao pressure traces diverge later in systole, and the maximal gradient occurs during the descent of the aortic pressure tracing. In contrast, with fixed obstruction (B), the LV and Ao pressure tracings diverge early, and the maximal gradient occurs during the blunted upstroke of the aortic pressure tracing. In both dogs, the pressure gradient increases *(solid arrows)* following a premature contraction *(open arrows)*. However, this phenomenon is more pronounced in the dog with dynamic obstruction. (Courtesy of Dr. David Sisson, University of Illinois.)

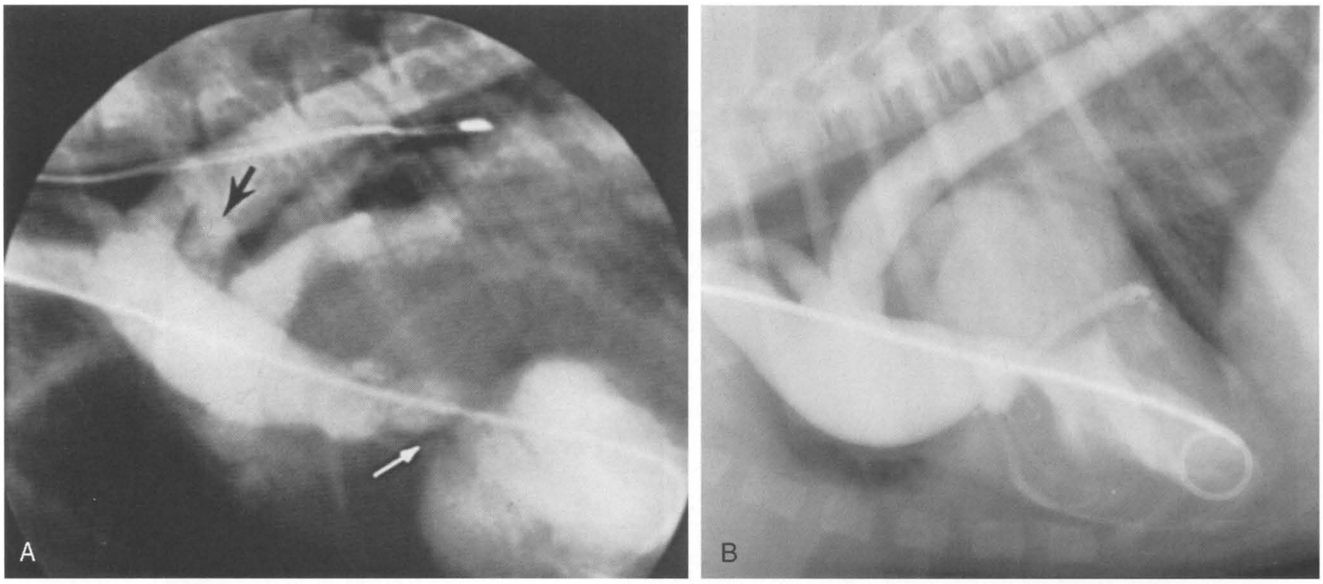


FIGURE 24–22

(A) Angiocardiogram from a cat with congenital subaortic stenosis and patent ductus arteriosus. Following injection of contrast into the left ventricle, a subvalvular obstruction *(white arrow)* is evident beneath the aortic valve. A large ductus arteriosus *(black arrow)* is evident and results in shunting of dye from the descending aorta into the main pulmonary artery. An esophageal stethoscope is noted in the dorsal thorax. (B) The canine study reveals a hypertrophied left ventricle with indentation of the papillary muscles into the lumen, a triangular subvalvular obstruction, and poststenotic dilatation of the ascending aorta and brachiocephalic trunk. There is also mitral regurgitation that outlines a dilated left atrium. (From Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 904, with permission.)

Surgery

Surgery has been employed to dilate, resect, or bypass the obstruction. However, such surgery has thus far been performed infrequently.[100–103, 103a, 103b]

Balloon Catheter Dilation (Valvuloplasty)

Balloon catheter dilation of the subaortic area has been used to reduce the severity of obstruction (Fig. 24–23).[104] In our experience in using this technique, an approximate 50 percent decrease in the gradient at the time of the procedure is typical (Figs. 24–20*B*, 24–24); however, in some dogs, this benefit attenuates over time. Nevertheless, this procedure merits consideration and further study because it can be done with very low mortality and morbidity.

Medical Therapy

Empiric medical therapy has been used in dogs with SAS (see Table 24–3). We prescribe beta-adrenergic blocking drugs, such as propranolol or atenolol, to dogs with a history of syncope (without CHF); with gradients of greater than 125 mmHg; or with significant ST-T changes or frequent ventricular extrasystoles noted on a postexercise or Holter ECG. Beta-adrenergic blockade can decrease maximal exercise heart rate, reduce ST-segment deviation, and decrease the overall frequency of ventricular extrasystoles, as well as decrease myocardial oxygen demand. However, the overall value of beta-blockade or calcium channel antagonists on clinical signs or longevity is unproved.

Should CHF develop, medical therapy with digoxin, furosemide, dietary sodium restriction, and nitrates is initiated. Low doses of angiotensin converting enzyme inhibitors may be prescribed, but any arterial vasodilator drug must be used with great caution in the setting of fixed outflow tract obstruction (chapter 12).

COARCTATION OF THE AORTA

Anomalies of the aorta that result in left ventricular outflow obstruction, in contrast to the situation in children, are rare in dogs and cats. *Coarctation* of the aorta is characterized by narrowing of the aorta distal to the subclavian artery, usually adjacent to the ductus arteriosus.[105] One reported case[106] showed systolic and diastolic murmurs and left ventricular failure. Clinical features of coarctation in children are well described and in many ways are similar to this case.[14]

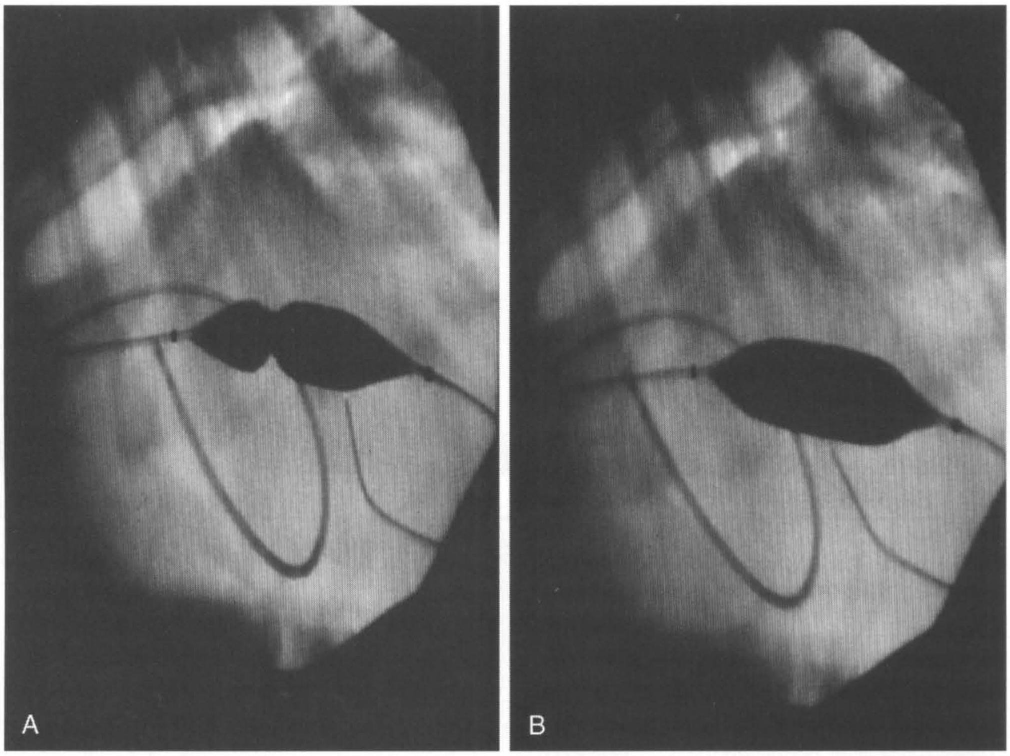


FIGURE 24–23

Catheter balloon dilation of a congenital subvalvular stenosis in a dog. A balloon-dilation catheter has been placed over a guide wire and centered within the left ventricular outflow tract. (The other catheter is positioned in the right side of the heart and proximal pulmonary artery.) (A) Partial inflation of the balloon demonstrates the "waist" of the stenotic ring. (B) Full inflation is evident. This intervention may partially relieve the obstruction by tearing portions of the subvalvular ridge.

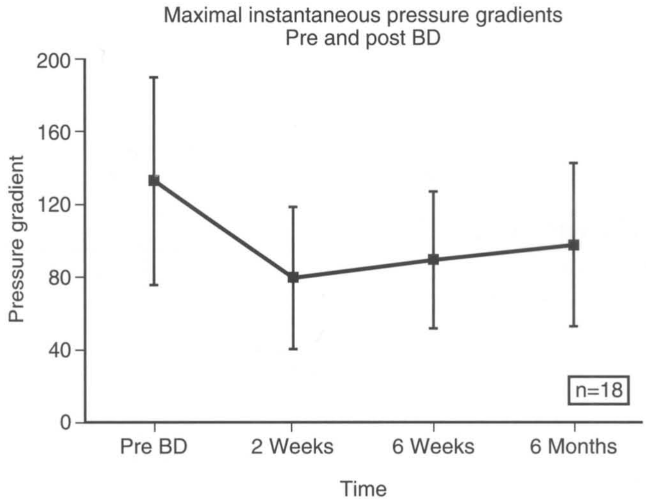


FIGURE 24–24

Results of balloon catheter dilation of subaortic stenosis on the maximal, instantaneous pressure gradients measured by Doppler echocardiography in 18 consecutive canine cases over a 6-month follow-up. Average pressure gradient (+/− SD) for the group is shown.

Tubular hypoplasia of the ascending aorta[107] and *aortic interruption*[108] also have been described in dogs. These lesions represent more extreme examples of obstructive malformation of the aorta with ventricular outflow obstruction. Definitive diagnosis usually requires angiography, though magnetic resonance imaging (MRI) and CT scanning are effective methods for evaluating lesions of the aortic arch. Surgical correction has been successful in affected dogs.

LESIONS CAUSING SYSTEMIC-TO-PULMONARY SHUNTING

ATRIAL SEPTAL DEFECTS

DEVELOPMENTAL ANATOMY

During cardiac development, the atria and ventricles are joined as a common chamber. The common atrioventricular canal is partitioned by growth of cardiac septa, resulting in the four-chambered heart (chapter 1). The atria are partitioned by septum I (primum) and septum II (secundum); the latter develops to the right of septum I (see Fig. 1–3). The foramen ovale, the slitlike passageway for blood that persists between these septa, permits right-to-left atrial shunting in the fetus, but closes functionally and anatomically in the neonate once left atrial pressure increases. Eventually, the lower atrial septum is connected to the upper ventricular septum by growth and differentiation of the endocardial cushions.

PREVALENCE. Defects in atrial septa I and II or maldevelopment of the endocardial cushions causes patencies of the atrial[14, 30, 33, 59, 109–116] or atrioventricular[4, 8, 117] septum. In the cat this is relatively common, comprising about 9% of congenital heart defects.[22] In the dog it is encountered sporadically,[5, 33, 34, 34a] with a frequency of 0.7 percent in a national data base. A precise genetic basis of disease has not been determined for either species.

LESIONS

GROSS MORPHOLOGY. An atrial septal defect (ASD) can be classified according to location of the malformation.[14] Defects of the septum located within the fossa ovalis caudal to the intervenous tubercle are called an *ostium* (or septum) *secundum defect* (see Figure 8–2).[109] Patency of the lower atrial septum represents an *ostium primum defect* (Fig. 24–25; see also Color Plate 6). The rare *sinus venosus defect* is found dorsocranial to the fossa ovale[112] (Figs. 24–25, 24–26; see also Figs. 1–3; 8–3 and Color Plate 5). Patent foramen ovale is not a true ASD inasmuch as the septa are anatomically formed; however, if the septa do not seal, the foramen may be pushed or stretched into an open position.[59] Thus, the principal significance of patent foramen ovale pertains to right-to-left shunting that may develop in animals with elevated right atrial pressures.

The ostium primum ASD is often very large, and this defect can contribute to a more complex and variable *atrioventricular septal defect* or *endocardial cushion defect*, so named because the endocardial cushions normally partition the fetal atrioventricular canal (Color

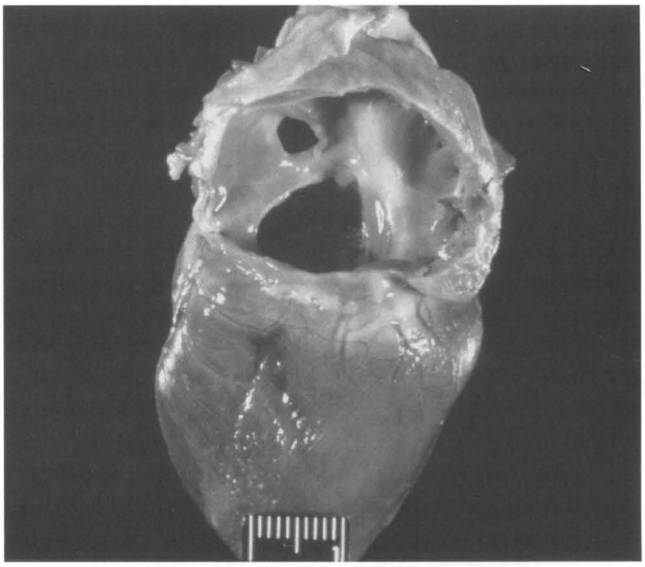


FIGURE 24–25

Gross pathologic specimen containing two atrial septal defects in a cat. The right atrial free wall has been removed to demonstrate a secundum (upper) defect caudal to the intervenous tubercle and a larger ostium primum defect within the ventral atrial septum.

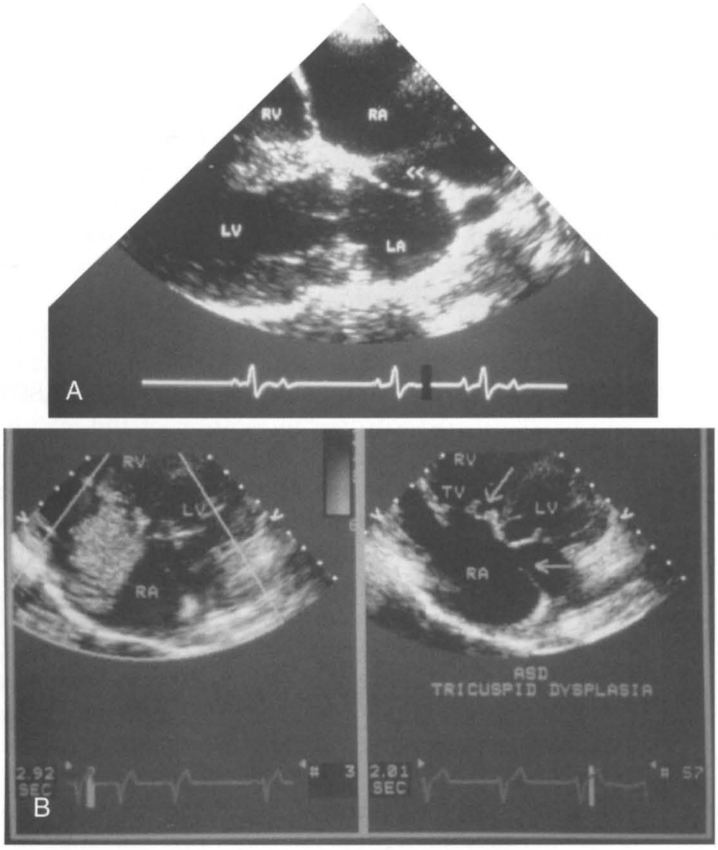


FIGURE 24–26

Atrial septal defects: echocardiographic anatomy. (A) Patent foramen ovale *(arrowheads)* in a dog with tricuspid valve malformation. The component portions of the atrial septum are present but have not fused because of the elevated right atrial pressures. Shunting in this case was from right atrium *(RA)* to left atrium *(LA)*. The right ventricle *(RV)* and the left ventricle *(LV)* are indicated. (B) Ostium primum atrial septal defect *(right panel)* and tricuspid valve *(TV)* malformation in a Doberman pinscher. The atrial septal defect is located in the lower portion of the atrial septum and is pointed out by a horizontal arrow. Bidirectional shunting was present in this case. *LV*, left ventricle; *RA*, right ventricle; *RV*, right ventricle (arrow in the RV points to the malformed tricuspid valve). The left panel is a black and white reproduction of a color Doppler echocardiogram that demonstrates a broad tricuspid regurgitation jet from the same image as the right panel.

Plate 6). Complete endocardial cushion defects include (1) a primum ASD, (2) a ventricular septal defect component, and (3) anomalous atrioventricular valves.[118] The latter often include a common septal leaflet that serves both ventricles.[13] These severe malformations are also called *atrioventricular septal defects*, *common atrioventricular canal*, and *canal defects*, since the primitive atrioventricular canal never partitions and there is communication between all four cardiac chambers (Fig. 24–26).[117] The common atrioventricular valve may contain clefts or notches, which predispose to valvular insufficiency. In some cases, lateral malalignment of the atrial and ventricular septa may occur such that the annulus of one atrioventricular valve straddles both ventricles.[118]

PATHOPHYSIOLOGY

The pathophysiology of isolated secundum ASD is summarized in Figure 24–27. Shunting depends on (1) the caliber of the orifice (defects small enough to maintain a differential pressure between the two connected chambers are termed *restrictive*), and (2) the relative resistances in the systemic and pulmonary

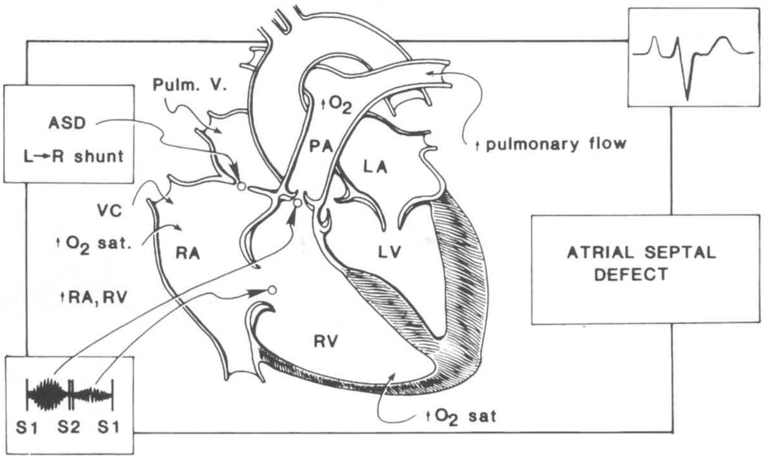


FIGURE 24–27

Pathophysiology and genesis of clinical findings in atrial septal defect (see text for details). (From Bonagura JD (ed). Cardiology. New York, Churchill Livingstone, 1987, with permission.)

circulations.[14] Typically, blood shunts from left-to-right. However, conditions that increase right atrial or ventricular pressures will retard left-to-right shunting and may lead to reversed (right-to-left) shunting. This can develop with severe pulmonic stenosis,[59] tricuspid atresia, tricuspid valve dysplasia (Fig. 24–26), or pulmonary hypertension.

The heart with a large ASD should be considered to have a single common atrium from which blood flows preferentially across the atrioventricular path of least diastolic resistance. Since the right ventricular walls are thinner and more distensible, more blood enters the right than the left ventricle (Fig. 24–27). The resultant volume overload of the right atrium (RA), right ventricle (RV), pulmonary artery (PA), and pulmonary veins leads to enlargement of these structures (Fig. 24–28). The left atrium receives more blood, but this chamber usually enlarges only slightly as the increased return is shunted immediately into the lower-pressure right atrium. When significant left atrial enlargement does occur, the possibility of an endocardial cushion defect with concurrent mitral regurgitation should be entertained.

Left-to-right shunting increases the hemoglobin oxygen saturation in the RA, RV, and PA. Although the low-velocity shunting of blood across the ASD does not cause a cardiac murmur, excessive transvalvular flow across the right-sided cardiac valves may generate murmurs of relative pulmonic and tricuspid stenosis (Fig. 24–29). Delayed closure of the pulmonic valve (and early closure of the aortic valve) causes splitting of the second heart sound. Since the right side of the heart is volume overloaded, right ventricular failure may develop in advanced cases. Complete endocardial cushion defects with mitral regurgitation may lead to left-sided or bilateral congestive heart failure. The patient with a large atrial septal defect and left-to-right shunt may develop high pulmonary vascular resistance leading to pulmonary hypertension, a condition termed *Eisenmenger's physiology* (discussed later). Whether animals with ASD require the relatively long time for development of pulmonary hypertension noted in humans with secundum ASD is unknown.[14]

CLINICAL FINDINGS

SIGNALMENT. The condition may be more common in cats than in dogs. Breed predispositions for atrial septal defects in dogs[34] are indicated in Table 24–1. The boxer is noted for prevalence of secundum defects.

CLINICAL SIGNS. Animals with small, uncomplicated, restrictive lesions are asymptomatic. In advanced cases with severe lesions, congestive heart failure may be evident.

PHYSICAL EXAMINATION. The typical left-to-right atrial septal defect may be characterized by a soft-to-moderate-intensity systolic murmur. The systolic murmur of relative pulmonic stenosis is easiest to identify. It is

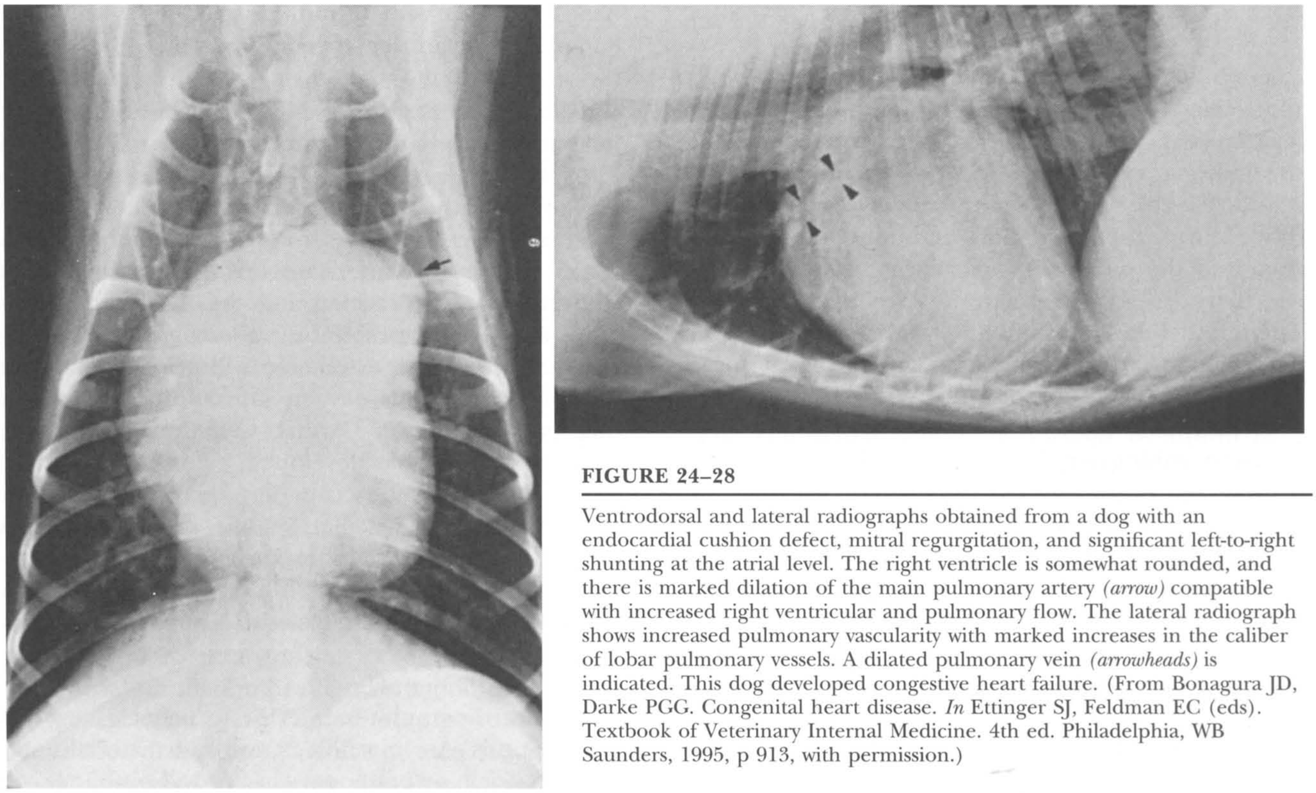


FIGURE 24–28

Ventrodorsal and lateral radiographs obtained from a dog with an endocardial cushion defect, mitral regurgitation, and significant left-to-right shunting at the atrial level. The right ventricle is somewhat rounded, and there is marked dilation of the main pulmonary artery *(arrow)* compatible with increased right ventricular and pulmonary flow. The lateral radiograph shows increased pulmonary vascularity with marked increases in the caliber of lobar pulmonary vessels. A dilated pulmonary vein *(arrowheads)* is indicated. This dog developed congestive heart failure. (From Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 913, with permission.)

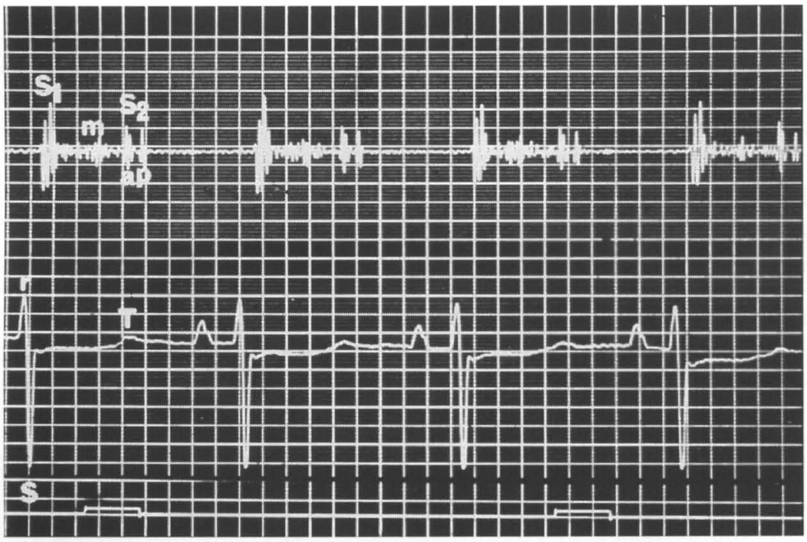


FIGURE 24–29

Phonocardiogram from a dog with atrial septal defect, demonstrating a systolic ejection murmur *(m)* and splitting of the second heart sound into aortic and pulmonic components. (Recording courtesy of Drs. David Smetzer and Robert L. Hamlin.)

heard best over the pulmonary valve and radiates dorsally into the pulmonary artery over the left, cranial cardiac base. When a systolic murmur of mitral regurgitation is identified over the left apex, an endocardial cushion defect with cleft mitral leaflet should be considered. Rarely, a diastolic rumble of relative tricuspid stenosis may be audible over the right hemithorax. Cyanosis is unexpected unless there is stenosis of a right-sided heart valve[59] or pulmonary hypertension, in which case the second heart sound should be tympanic. Differential diagnosis includes *anomalous pulmonary venous return* to the right atrium, which leads to functional circulatory disturbances similar to an ASD.[119]

RADIOGRAPHY. In the typical ASD, the right atrial and ventricular volume overloading and secondary right ventricular hypertrophy should be evident by reviewing the thoracic radiograph and echocardiograph (Figs. 24–26, 24–28). The main pulmonary artery may be dilated from increased flow or pulmonary hypertension, and the pulmonary vascularity is increased (unless there is elevated pulmonary vascular resistance). The left atrium is normal to slightly enlarged. Prominent left atrial enlargement suggests mitral insufficiency from a cleft mitral valve.

ECHOCARDIOGRAPHY. In addition to defining and confirming the radiographic changes just described, the septal defect may be imaged as an area of abnormal sonolucency (see Figs. 8–2, 8–3). However, care must be taken not to overdiagnose atrial septal defects based on this finding alone, since normally, "echo dropout" occurs in the area of the fossa ovale. M-mode studies demonstrate paradoxic ventricular septal motion owing to right-sided volume overload. Saline contrast echocardiography may traverse the defect when there is bidirectional shunting. Doppler studies are useful to identify (1) abnormal blood flow through the defect, (2) increased transpulmonic or transtricuspid velocity secondary to increased blood flow, or (3) mitral insufficiency. Quantitative Doppler studies can be used to estimate the shunt ratio (Qp:Qs), although the spectral dispersion and turbulence recorded in the main pulmonary artery are limitations of this technique.[54]

ELECTROCARDIOGRAPHY. The ECG can be normal, or it can demonstrate right atrial or right ventricular enlargement (Fig. 24–30). Arrhythmias or intraventricular conduction disturbances can occur.[111] Right bundle branch block or a left cranial axis deviation has also been observed with ostium primum ASD and more complex atrioventricular septal defects.

CARDIAC CATHETERIZATION. This can be used to diagnose the condition, recognize concurrent lesions, and estimate the magnitude of shunting. The cardiac catheter often is advanced across septal defects since many are quite large. By measuring oxygen content in the venae cavae, cardiac chambers, and great vessels, shunting can be detected and the magnitude of systemic-to-pulmonary shunting estimated. Note, however, that the shunt estimation will be affected by the variability of venous oxygen saturation found in the dog (see section on Cardiac Catheterization in this chapter). If CHF has developed, central venous, right atrial, and right ventricular diastolic pressures are increased. Right ventricular systolic pressure is either normal or elevated when there is pulmonary hypertension or a large left-to-right shunt. High flow across the pulmonic valve causes "relative" pulmonic stenosis, identified in most cases by a pressure gradient of between 5 and 20 mmHg.

Angiocardiography is inferior to echocardiography for diagnosis. An injection of contrast material in the right ventricle or pulmonary artery will outline left-to-

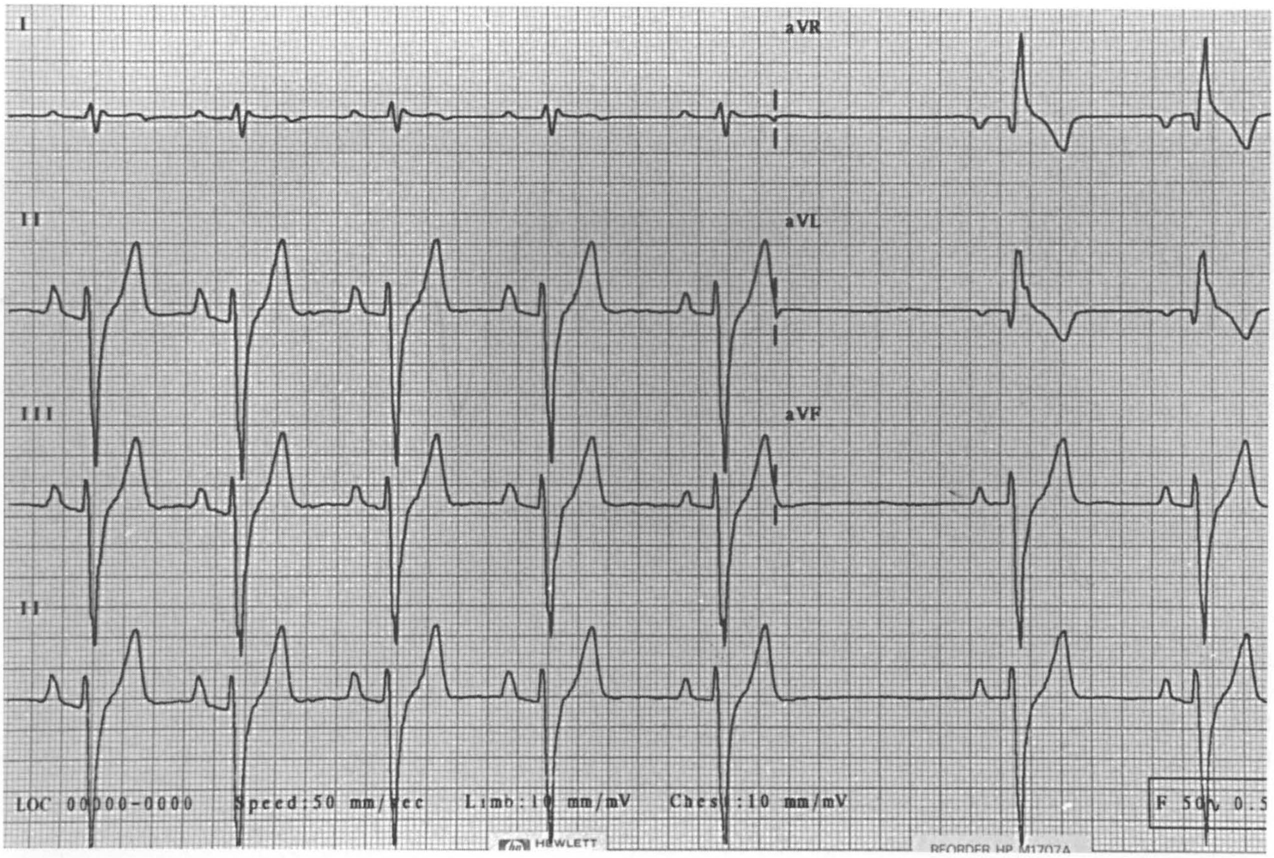


FIGURE 24–30

Electrocardiogram from a dog with atrial septal defect. The P waves are enlarged and widened, compatible with atrial dilatation with a prominent Ta wave (see chapter 6). An axis deviation in the frontal plane is evident, with depolarization oriented cranially and slightly to the right (note lead aVR); also, terminal forces (S wave) are prolonged, compatible with right ventricular conduction delay from right ventricular dilatation. Secondary T-wave changes are also evident.

right shunting defects during the left-sided phase of the study. Following pulmonary venous return, the atrial septum usually can be seen between the left atrium and aorta on the lateral projection. Viewing this area for a jet of contrast or, more commonly, a "spilling-over" of dye across this wall into the right atrium, auricle, and venae cavae, permits shunt identification. With endocardial cushion defects, a left ventriculogram may outline a VSD, mitral regurgitation, and possibly left ventricular–to–right atrial shunting.

NATURAL HISTORY

The secundum type of ASD often is well tolerated. Primum defects or endocardial cushion defects, in our experience, are more likely to lead to right-sided or biventricular congestive heart failure or pulmonary hypertension. Should severe pulmonary vascular disease develop, Eisenmenger's physiology may occur (see later). Atrial fibrillation or other arrhythmias can complicate these conditions. The overall prognosis for cats with endocardial cushion defects is guarded to poor, as most cats develop severe cardiomegaly and die of congestive heart failure. If CHF occurs, life can be prolonged with medical therapy using overall management strategies similar to those for animals with ventricular septal defects.

VENTRICULAR SEPTAL DEFECTS

DEVELOPMENTAL ANATOMY

The ventricular septum is formed by fusion of a number of primordial components (see Fig. 1–3). The fully developed ventricular septum consists of two general parts. One is a small, dorsal, membranous portion that forms part of the fibrous skeleton of the heart and is located between the right ventricular inflow and outflow tracts; the other is an extensive muscular septum that forms the inlet and outlet tracts of the ventricles, consisting of (1) the atrioventricular septum, (2) inlet septum, (3) apical and cranial (outflow) "trabecular" septal segments, and (4) infundibular (outlet) septum (Fig. 24–31).[118] Anomalous develop-

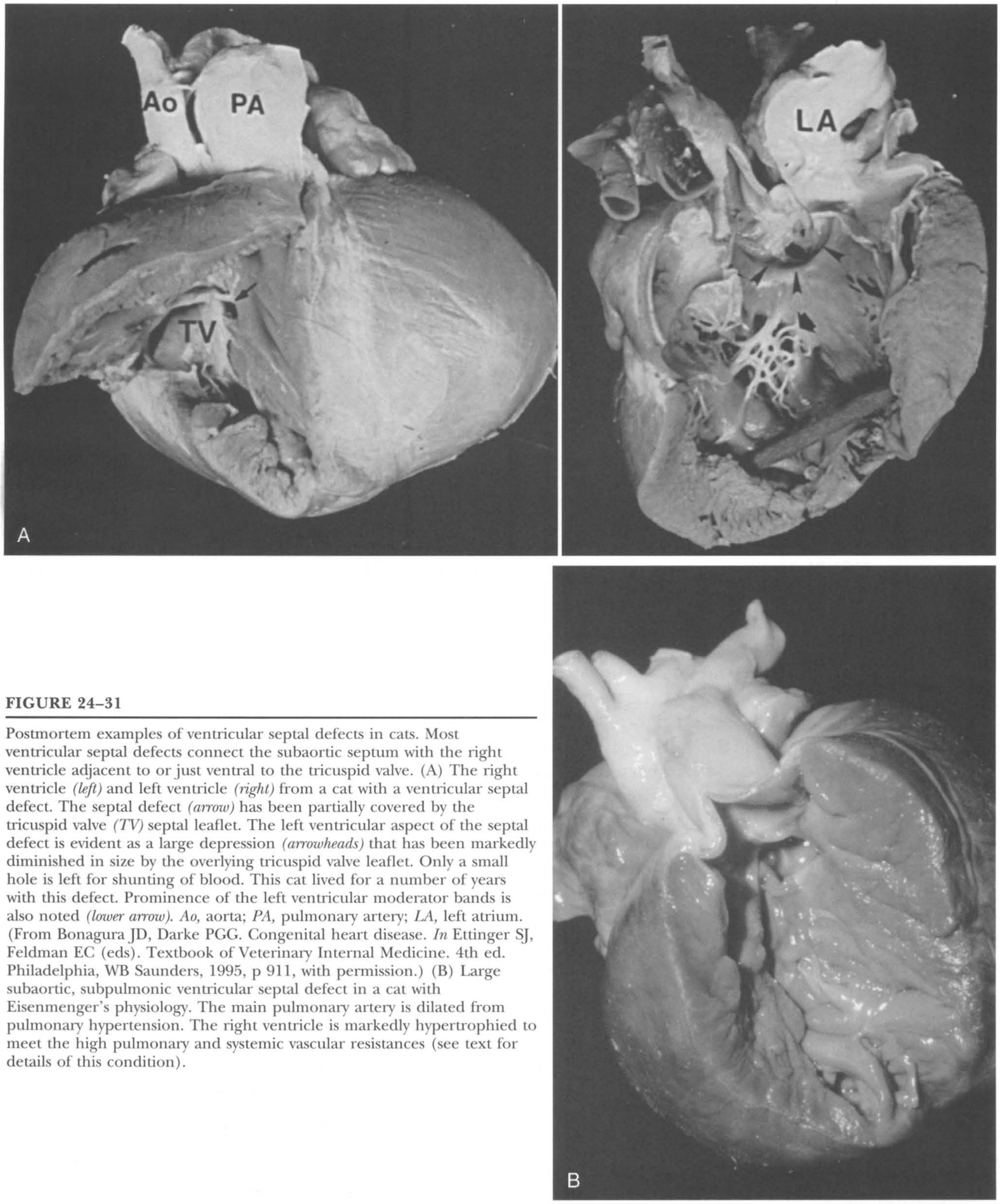


FIGURE 24–31

Postmortem examples of ventricular septal defects in cats. Most ventricular septal defects connect the subaortic septum with the right ventricle adjacent to or just ventral to the tricuspid valve. (A) The right ventricle *(left)* and left ventricle *(right)* from a cat with a ventricular septal defect. The septal defect *(arrow)* has been partially covered by the tricuspid valve *(TV)* septal leaflet. The left ventricular aspect of the septal defect is evident as a large depression *(arrowheads)* that has been markedly diminished in size by the overlying tricuspid valve leaflet. Only a small hole is left for shunting of blood. This cat lived for a number of years with this defect. Prominence of the left ventricular moderator bands is also noted *(lower arrow)*. *Ao,* aorta; *PA,* pulmonary artery; *LA,* left atrium. (From Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 911, with permission.) (B) Large subaortic, subpulmonic ventricular septal defect in a cat with Eisenmenger's physiology. The main pulmonary artery is dilated from pulmonary hypertension. The right ventricle is markedly hypertrophied to meet the high pulmonary and systemic vascular resistances (see text for details of this condition).

ment of any septal component may persist as a ventricular septal defect (VSD).

PREVALENCE. The frequency of isolated VSDs in dogs with congenital heart disease is estimated to be about 7%.[5, 33, 34] In cats,[22] the lesion has been observed in approximately 15 percent of those with congenital cardiac anomalies. The cause of most VSDs is unknown. Aside from its genetic basis in keeshonden with malformations of the infundibular, conotruncal septum[9, 24, 26] and the frequent occurrence of VSD in some breeds of dogs (Tables 23–9; 24–1), there are no consistent data about etiopathogenesis of spontaneous defects in dogs or cats.

LESIONS

Most VSDs are located dorsally or "high" on the ventricular septum and usually include a portion of the membranous septum (Figs. 24–31 to 24–34).[9, 24–26, 43, 120–129] In contrast, ventrally or apically positioned defects of the muscular ventricular septum are uncommon in small animals. Defects of the atrioventricular septum were described previously with ASD.

GROSS MORPHOLOGY. Ventricular septal defects may be classified according to location. The *left ventricular location* of the typical VSD is below the aortic valve. The *right ventricular location* of a VSD varies and is used to classify the defect, although the nomenclature is neither uniform nor simple.[14, 118] A helpful system often used in echocardiography involves recognizing septal defects of the right ventricular inflow or outflow tracts. This is based on a short-axis tomogram and a right parasternal long-axis view that includes the aorta and the right ventricular inlet. The typical defect in small animals is perimembranous (or paramembranous) (see Figs. 8–17*A*; 24–32). Thus, most VSDs will be found adjacent to the septal leaflet of the tricuspid valve or just below the valve on the inlet septum. The defect may be partially occluded by this valve or by fibrous connective tissue that develops along the right ventricular surface.

Defects are of varying size, but are often very large, and they may involve the infundibular (outlet) septum. Such defects are also termed "supracristal" (craniodorsal to the supraventricular crest), "subpulmonic" (below the pulmonic valve), or "subarterial." A VSD also may involve *malalignment* of components of the ventricular septum, a developmental aspect described previously (see Atrial Septal Defect) and later under Tetralogy of Fallot. Infundibular (subarterial) defects and large, perimembranous defects can predispose to prolapse of the right coronary cusp or the entire aortic root into the defect (Fig. 24–33). Because such prolapse can partially occlude the septal defect, aortic valve incompetency may develop as a complication.[4, 43] Rarely, defects may lie in the muscular ventricular septum (see Fig. 8–17*B*).

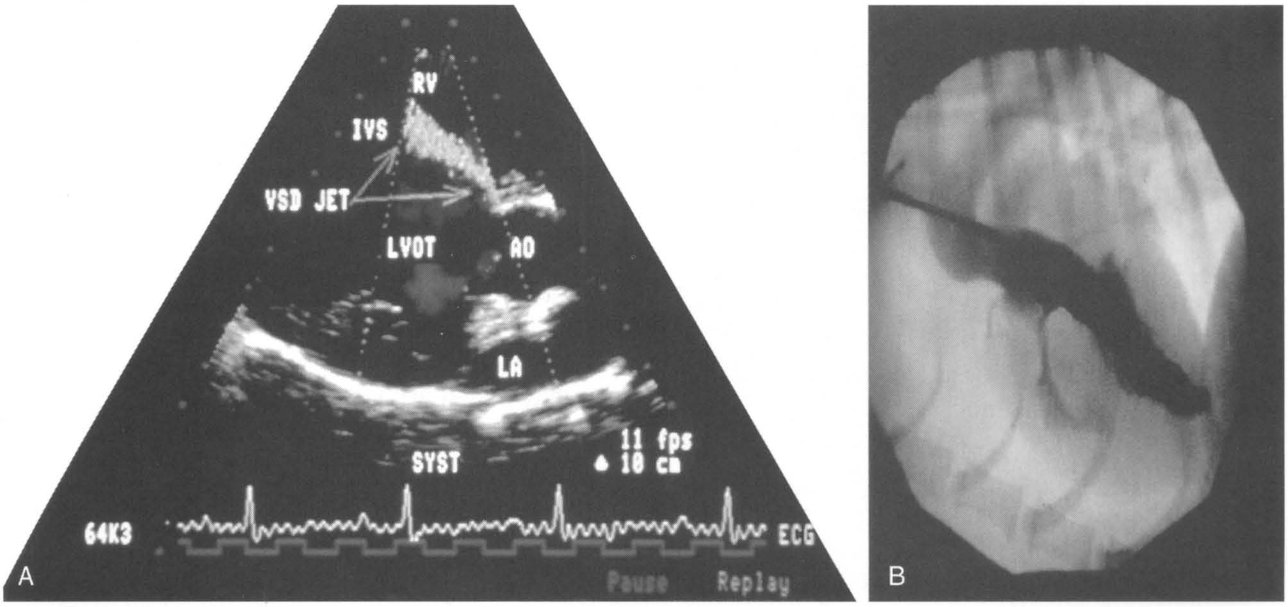


FIGURE 24–32

Perimembranous ventricular septal defects (VSD). (A) A left-to-right shunt *(arrows)* can be seen in this black and white reproduction of a color Doppler echocardiogram. The jet originates just ventral to the aortic root and is directed eccentrically toward the right ventricular apex. *LVOT*, left ventricular outflow tract; *Ao*, aorta; *LA*, left atrium; *IVS*, interventricular septum; *RV*, right ventricle; *syst*, systole. (B) Left ventricular angiocardiogram from another dog demonstrates a small, left-to-right shunting ventricular septal defect. Note the origin of the jet at the base of the aorta.

PATHOPHYSIOLOGY

Left-to-right shunting develops as the pulmonary vascular resistance drops following birth. It has been demonstrated that with "high" ventricular septal defects, much of the shunt flow is pumped across the defect and immediately into the pulmonary artery, with variable volumes ejected into the right ventricular chamber.[130, 131] Thus, the left ventricle—not the right ventricle—does most of the additional volume work. Additionally, as pulmonary flow increases, there is increased venous return to the left atrium and left ventricle, and the left ventricular diastolic pressure can increase. Left ventricular failure is likely when the left-to-right shunt is great (e.g., greater than 2.5:1, pulmonary to systemic flow). Even in small defects (e.g., Qp:Qs <1.5:1), the left heart will be enlarged since it carries up to 50 percent more blood than normal (Fig. 24–35).

The degree of right ventricular hypertrophy and the magnitude of left-to-right shunting depend on a variety of factors: size and location of the septal defect, pulmonary vascular resistance, and pulmonic valve function. Very large, unrestrictive defects cause the two ventricles to behave as a common chamber, so that ventricular pressures equilibrate and substantial right ventricular hypertrophy will be evident. Blood then follows the path of least resistance. If the pulmonary valve, pulmonary vascular resistance, and left-sided heart valves are all normal, tremendous shunting is likely to occur, and left-sided volume overload and CHF are expected consequences. Should pulmonary vascular resistance increase, then left-to-right shunting will be diminished and bidirectional shunting may be observed. In the animal with tetralogy of Fallot, the stenotic pulmonic valve or outflow tract offers such great resistance that right-to-left shunting predominates. Infundibular right ventricular hypertrophy leading to subpulmonic stenosis can develop as a complication of VSD in children, and a similar complication has been suspected in some small animals.

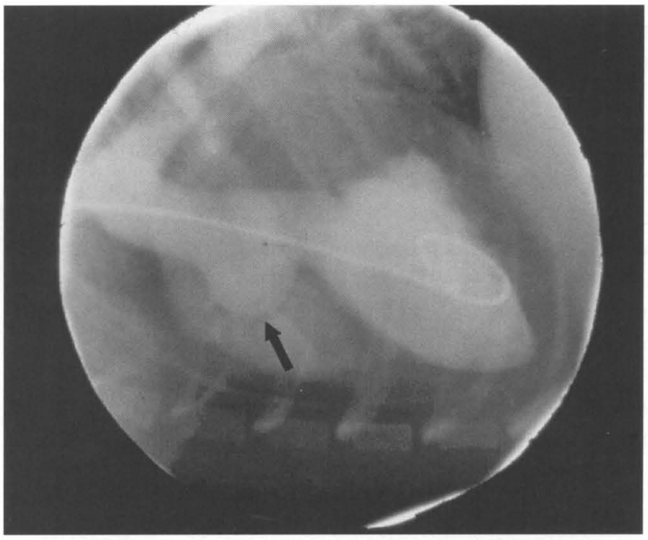


FIGURE 24–34

Left ventricular angiogram from another dog with prolapse of an aortic valve into a ventricular septal defect (*arrow*). A portion of the right ventricle is opacified from left-to-right shunting.

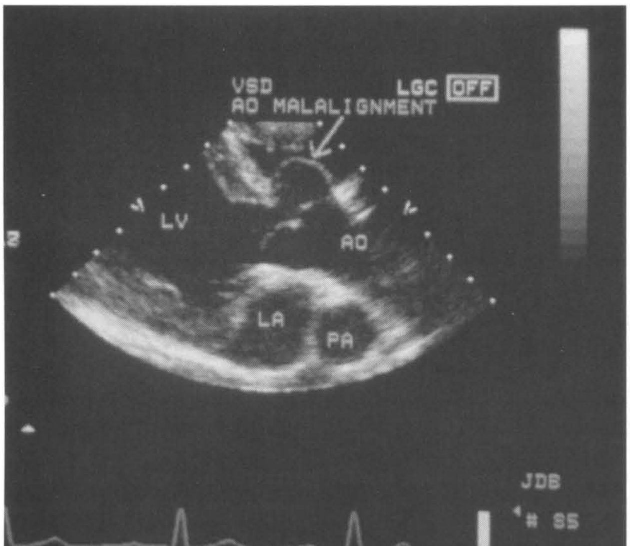


FIGURE 24–33

Paramembranous ventricular septal defects (VSD) with prolapse of an aortic valve cusp. Two-dimensional echocardiogram from a springer spaniel demonstrates a large VSD with prolapse of an aortic cusp (*arrow*) into the defect. In this case, the aortic root was also malaligned, with the ventricular outlet septum producing some "overriding" of the aorta. *AO*, aorta; *PA*, pulmonary artery; *LV*, left ventricle; *LA*, left atrium.

CLINICAL FINDINGS

SIGNALMENT. A number of canine breeds are predisposed to VSD (see Tables 23–9; 24–1). Ventricular septal defects are among the most common cardiac malformations in the cat.

CLINICAL SIGNS. Animals with small, uncomplicated, restrictive VSDs are generally asymptomatic. More advanced or complex lesions may cause signs associated with their pathophysiology.

PHYSICAL EXAMINATION. Clinical features of VSD are variable and related to the degree and direction of shunting. The cardinal sign of the left-to-right shunting, perimembranous (subcristal) lesion is a harsh, holosystolic murmur heard best along the cranial right sternal border.[93, 120] A systolic ejection murmur of relative pulmonic stenosis and, infrequently, splitting of the second heart sound may be evident at the left base. The murmur will be loudest over the left craniodorsal heart base when the communication is

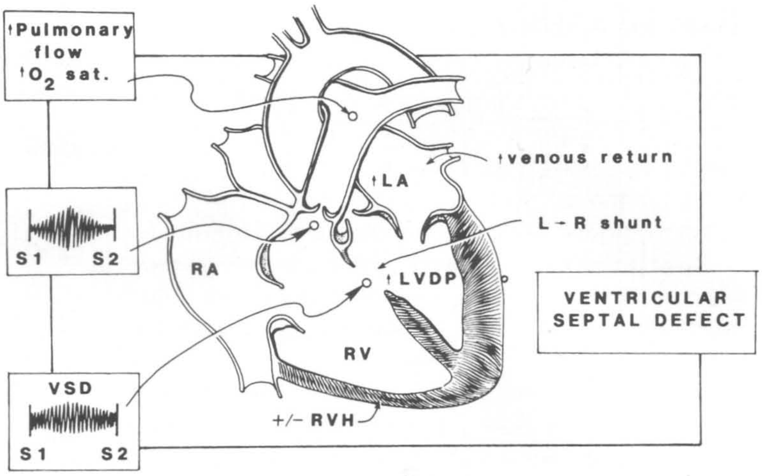


FIGURE 24–35

Pathophysiology and genesis of clinical findings in ventricular septal defect (see text for details). (From Bonagura JD (ed). Cardiology. New York, Churchill Livingstone, 1987, with permission.)

subpulmonic (supracristal). When a diastolic murmur of aortic regurgitation is present, prolapse of an aortic cusp should be suspected (Figs. 24–33, 24–34). Features of the atrioventricular septal defect were previously discussed (see Atrial Septal Defect).

RADIOGRAPHY. Thoracic radiographs are variable with VSD, but they usually demonstrate pulmonary overcirculation, left atrial and ventricular dilation, and variable degrees of right ventricular enlargement (Fig. 24–36).[6, 7, 36, 43, 132] The main and lobar pulmonary arteries often are dilated. If the shunt is left to right, then peripheral pulmonary vascularity is increased. With cases of VSD and high-resistance pulmonary hypertension, the main and proximal lobar vessels are often distended, but the peripheral vascular markings are scant.

ELECTROCARDIOGRAPHY. Findings are also variable but may indicate left atrial enlargement, left ventricular dilation, and/or right ventricular hypertrophy. The frontal plane leads often demonstrate abnormal early ventricular septal activation, characterized by a Q wave that is wide or contains high-frequency notching; this can be a subtle but helpful abnormality (Fig. 24–37). The presence of a right axis deviation with VSD often indicates a large defect with equilibration of ventricular pressures, concurrent pulmonic stenosis, or pulmonary hypertension.

ECHOCARDIOGRAPHY. In most cases echocardiography successfully delineates the defect (see Figs. 8–17; 24–32*A*). Both standardized and angled views should be evaluated to record the septal defect diameter maximally and identify the right ventricular entry location. Dimensional increases typical of volume overloading of the left atrium and left ventricle are common findings. Occasionally, the RV wall is hypertrophied, even in the setting of a relatively restrictive VSD with normal pulmonary artery pressures. Doppler echo studies can identify the high-velocity jet of a restrictive VSD (Fig. 24–38). Color-coded Doppler or saline contrast studies

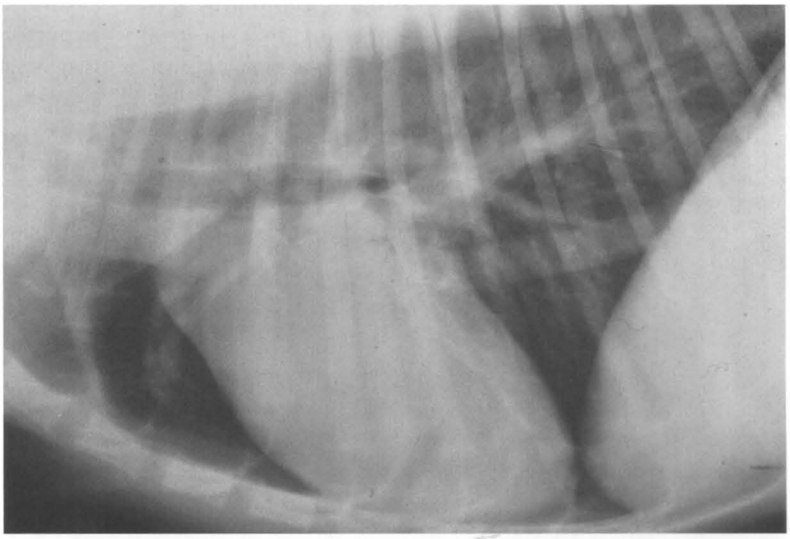


FIGURE 24–36

Lateral radiograph from an Irish setter with a left-to-right shunting ventricular septal defect (VSD). There is left ventricular and left atrial enlargement and prominent pulmonary vascularity. The radiographic features of VSD are quite variable, influenced by size and location of the defect and the pulmonary artery pressure. Accordingly, different degrees of left-sided, right ventricular, and pulmonary artery enlargement can be observed.

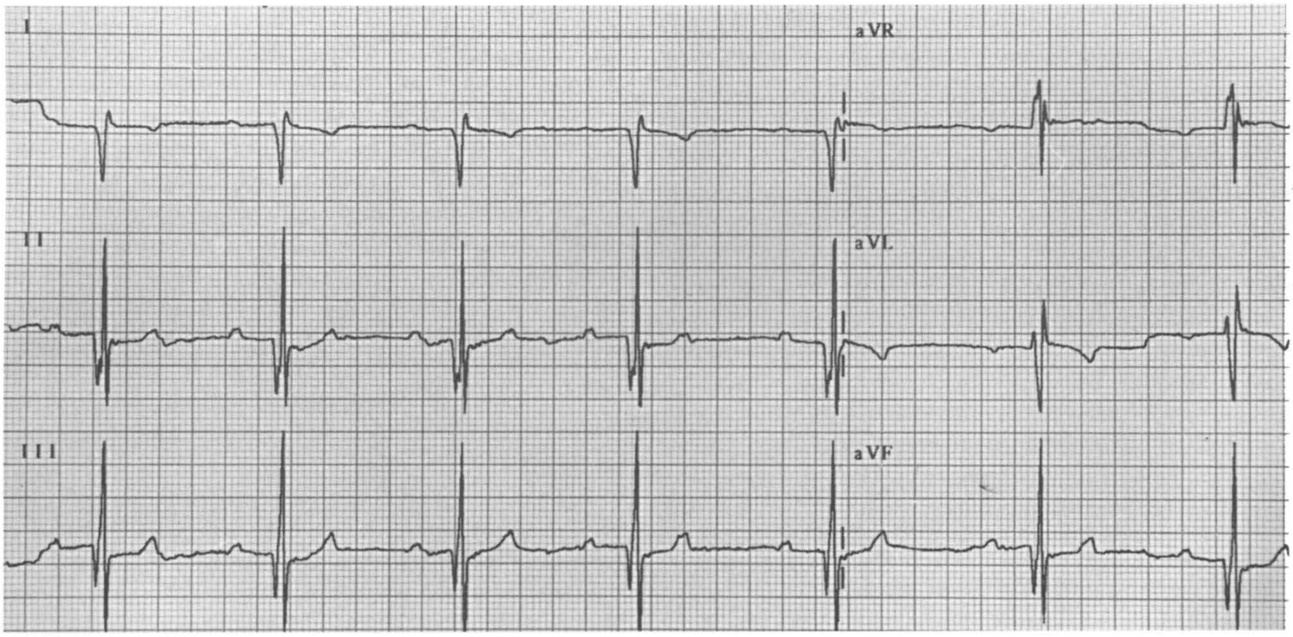


FIGURE 24–37

Electrocardiogram from a dog with a ventricular septal defect. An intraventricular conduction disturbance, characterized by abnormally wide, deep, and notched Q-waves in the left and caudal leads, is not uncommon in this condition.

(see Figs. 8–2, 8–3, and Color Plates 8 and 9) can be utilized to demonstrate shunting. The pressure drop across the defect can be estimated from the peak shunt velocity using the Bernoulli formula, $\Delta P = 4V^2$. Provided there is no aortic stenosis, the right ventricular systolic pressure can be estimated noninvasively as follows: measure the systolic arterial pressure using an oscillometric or Doppler flow device; calculate the pressure drop across the VSD; and subtract the pressure drop from the systolic arterial pressure.[54] Echocardiographic data are useful in formulating a prognosis for the isolated defect. The following findings are generally favorable for longevity: (1) maximal defect diameter from orthogonal planes using high-quality 2-D echocardiography less than 40 percent that of the aorta; (2) maximal velocity of the left-to-right shunt greater than 4.5 m/s; (3) estimated right ventricular systolic pressure less than 45 mmHg; (4) significant aortic regurgitation not evident.

CARDIAC CATHETERIZATION. Cardiac catheterization and angiocardiography in cases of VSD document the anatomic lesions and estimate the degree of shunting. An oxygen step-up is recorded in the right ventricle. Left ventricular diastolic pressures are elevated with ventricular failure or severe diastolic overload. A systolic pressure gradient across the pulmonic valve of 5 to 20 mmHg, indicating relative pulmonic stenosis, is typical with left-to-right shunting VSD. Pulmonary hypertension and elevated right ventricular systolic pressure are detected in some cases. Since pulmonary hypertension can be caused by pulmonary vascular disease (Eisenmenger's reaction),[14] high Qp:Qs, left-sided CHF, or a combination of these factors, attention

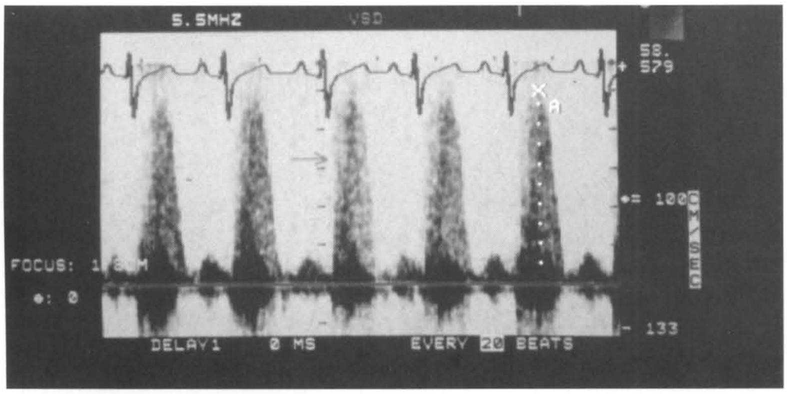


FIGURE 24–38

Continuous-wave Doppler echocardiographic recording obtained from a dog with a left-to-right shunting ventricular septal defect. The shunt flow is toward the transducer, producing a positive, high-velocity signal. Slightly denser velocity spectra located closer to the baseline are caused by red blood cells flowing toward the defect. The highest velocities develop within and immediately distal to the defect. In this case, the peak velocity approximates 5 m/sec (estimated gradient, approximately 100 mmHg), indicating maintenance of the left-to-right ventricular pressure gradient and a "restrictive" lesion.

must be directed to shunt estimation by oximetry, calculation of pulmonary vascular–to–systemic resistance ratio, and measurement of pulmonary capillary wedge pressure (see earlier; also chapter 9).

The angiocardiogram (Figs. 24–32*B*, 24–34; see also Fig. 9–12*B*) may outline the defect as well as anatomic lesions or enlargements of the ventricles and great vessels. Aortic regurgitation may be observed following a supravalvular aortic injection.[43, 99] Associated defects such as subaortic stenosis, mitral valve dysplasia, pulmonic stenosis, and patent ductus arteriosus may occasionally be observed.

Catheterization and angiographic findings favoring a good prognosis for life include: (1) Qp:Qs ratio less than 1:5; (2) normal pulmonary capillary wedge and left ventricular end-diastolic pressures; (3) normal or minimally elevated pulmonary artery pressures; (4) normal-to-minimally elevated pulmonary vascular resistance ratio; (5) absence of substantial aortic regurgitation; and (6) absence of concurrent malformations.

NATURAL HISTORY

Potential outcomes of a ventricular septal defect include

- Tolerance of the lesion by the patient;
- Development of CHF;
- Partial or complete closure of a VSD[123] by adherence of the septal tricuspid leaflet, right ventricular hypertrophy, aortic valve prolapse, or exuberant fibrous connective tissue that forms a ventricular septal aneurysm;
- Progressive aortic regurgitation due to valve prolapse;
- Development of progressive subpulmonic and infundibular outflow obstruction;
- Development of pulmonary vascular disease and pulmonary hypertension[133]; and
- Reversal of the shunt with development of arterial hypoxemia and cyanosis.[30, 77]

If heart failure is to occur, it is most likely to develop at the time resistance falls; therefore, most pups will develop CHF before 8 weeks of age. The reality is that such pups usually die before they are examined by a veterinarian, and those animals that survive to 4 months are probably a biased population from which to judge the true prognosis of these lesions. It is more difficult to predict the survival of an older animal without additional studies. Detailed Doppler echocardiographic studies and/or catheterization data, as described earlier, permit more accurate prognostication. The great majority of dogs that live to 6 months of age without clinical signs will survive for many years.

CLINICAL MANAGEMENT

Numerous methods are available to manage atrial and ventricular septal defects. Most small animals that have survived through the vaccination series without clinical signs usually tolerate the defect and do not require therapy.

Surgery

Definitive treatment of symptomatic or severe lesions requires surgery using cardiopulmonary bypass.[122, 134] Pulmonary artery banding can be used to create supravalvular pulmonary stenosis and decrease the magnitude of left-to-right shunting.[125, 135] This procedure is recommended only (1) when signs of left-sided congestive heart failure occur, or (2) with documented moderate-to-severe pulmonary hypertension caused by high flow and with a calculated pulmonary-to-systemic resistance ratio of 0:6 or less. Anemia should be avoided, since a low hematocrit leads to decreased pulmonary vascular resistance and increased shunting.[136]

Medical Therapy

When left-sided CHF occurs, digoxin and furosemide are indicated (see Table 24–3). Arterial vasodilators such as enalapril and hydralazine may be beneficial since they decrease systemic resistance and also decrease left-to-right shunting.[137] The prognosis for Eisenmenger's syndrome is very poor as discussed later.

PATENT DUCTUS ARTERIOSUS

DEVELOPMENTAL ANATOMY

The ductus arteriosus is derived from the left sixth aortic arch. It shunts blood from the pulmonary artery to the descending aorta, an action that diverts flow from the collapsed fetal lung. Following parturition, the increase in oxygen tension leads to inhibition of local prostaglandins, causing functional closure of the ductus, followed by anatomic obliteration during the ensuing weeks of life. Initial closure, probably accomplished by contraction of smooth muscle within the ductus,[138] decreases ductal flow dramatically within the first 12 to 14 hours of life. Although the ductus may be probe-patent in pups less than 4 days of age, it generally closes by 7 or 8 days postwhelping, with histologic studies suggesting even earlier closure.[23, 139, 140]

PREVALENCE. This disorder has been extensively described in dogs and cats.[23, 33, 61, 139–158] Abnormal patency of the ductus is the most common defect in most surveys of canine congenital cardiovascular disease,[5, 33, 34] ranging in prevalence from about 25 to 32 percent of reported malformations (see also Table 23–6). Patent ductus arteriosus (PDA) is far less common in

cats, with a reported frequency of about 11 percent of cases with congenital heart disease.

LESIONS

GROSS MORPHOLOGY. Failure of ductal closure (Fig. 24–39) probably results from histologic differences within the wall of the ductus. Whereas the ductal wall contains a loose branching pattern of circumferential smooth muscle in normal pups, with PDA the wall more closely resembles that of the elastic aorta. The increasing genetic liability to PDA represents "extension of the noncontractile wall structure of the aorta to an increasing segment of the ductus arteriosus, progressively impairing its capacity to undergo physiologic closure."[159] The simplest form of this malformation is the ductus diverticulum, a blind, funnel-shaped outpouching of the ventral aspect of the descending aorta. Although this lesion can be recognized only by angiography or at necropsy, it represents the *forme fruste* of PDA and indicates that the dog possesses genes for this defect.[23] Increasing genetic liability results in PDA with left-to-right shunting, or the less common, but more severe, reversed PDA in which pulmonary hypertension develops, causing bidirectional or right-to-left flow through the ductus. Patent ductus arteriosus may also be identified in animals with complex forms of congenital heart disease and in some but not all cases of pulmonary atresia, in which, pulmonary flow may be supplied by the ductus or bronchial arteries.[30, 31, 107, 160] The mode of transmission of PDA is polygenic,[1, 23, 159] and the condition is observed in many breeds (see Table 24–1).

PATHOPHYSIOLOGY

The pathophysiology of PDA is summarized in Figure 24–40,[115] and modes of shunting are illustrated in Figure 24–41. Owing to the higher aortic than pulmonary blood pressure, blood shunts continuously into the main pulmonary artery. This results in a continuous cardiac murmur, increased pulmonary flow, and increased venous return to the left atrium and left ventricle. Volume overloading of the left side of the heart causes atrial dilatation, ventricular dilatation, and hypertrophy, and increases left ventricular diastolic pressure. If the luminal defect is large and the pulmonary vascular resistance relatively normal, left ventricular failure with pulmonary edema develops from volume overload. The left ventricular stroke volume increases as a result of increased filling contributing to an increased aortic systolic pressure. Aortic diastolic pressure is low owing to runoff of blood through the ductus. This causes a hyperkinetic, or water-hammer, arterial pulse. Increased volume flow in the aorta and pulmonary artery, combined with turbulence about the ductus, causes dilation of the aorta and main pulmonary artery. The right ventricle is spared unless there is pulmonary hypertension, in which case ventricular hypertrophy develops.

In a small percentage of cases, the lumen of the PDA is so large that pulmonary vascular pressure and resistance markedly increase. In Patterson's colony, this type of ductus was the most severe, and reversal of the shunt developed within the first months of life.[23, 159] This appears to fit the clinical picture in the dog, in which documentation of shunt reversal after 6 months of age is lacking.[154, 157, 161] Dogs and cats with reversed PDA exhibit high pulmonary vascular resistance, high

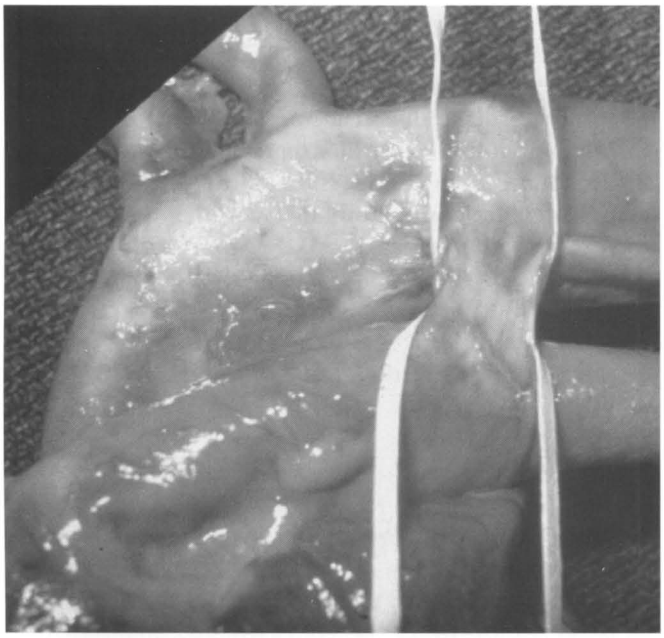


FIGURE 24–39

Persistent patent ductus arteriosus delineated by umbilical tape sutures. The ductus connects the descending aorta above with the pulmonary artery below.

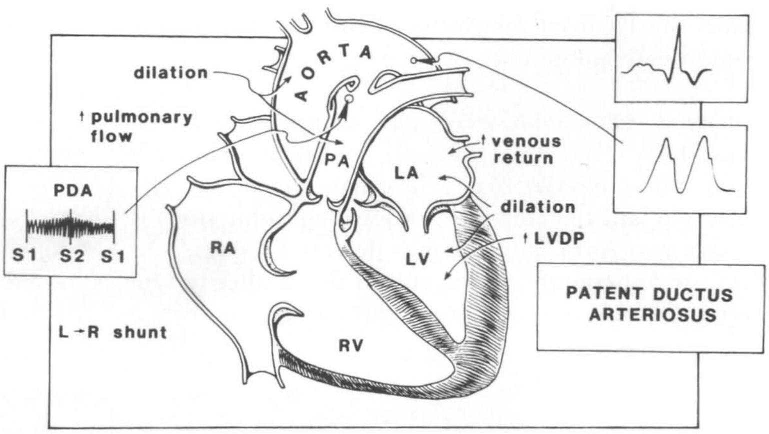


FIGURE 24–40

Pathophysiology and genesis of clinical findings in patent ductus arteriosus. See text for details. (From Bonagura JD (ed). Cardiology. New York, Churchill Livingstone, 1987, with permission.)

(systemic) pressures in the right ventricle and pulmonary artery, decreased pulmonary flow, a small left ventricle, and hypertrophy of the right ventricle. This reversal represents a form of Eisenmenger's physiology, which is discussed later.

CLINICAL FINDINGS

SIGNALMENT. Breeds at greatest risk for development of PDA include the Chihuahua, collie, Maltese, poodle, Pomeranian, English springer spaniel, keeshond, bichon frise, Cavalier King Charles, and Shetland sheepdog (see Tables 23–6; 24–1).[34] Many other breeds, including larger dogs such as the German shepherd, Newfoundland, and Labrador retriever, are prone to PDA in some regions. Females developed PDA at a rate of 2.49 per 1000 versus 1.45 per 1000 for males.[5]

Left-to-Right–Shunting Patent Ductus Arteriosus

CLINICAL SIGNS. Pups may be clinically healthy or thin and may demonstrate signs of left-sided congestive heart failure. Clinical signs are unlikely to occur until the pulmonary vascular resistance declines. The clinical features of PDA have been well-described (Fig. 24–40).

PHYSICAL EXAMINATION. In the usual case, the arterial pulses are hyperkinetic, a continuous thrill may be palpated at the craniodorsal cardiac base, and a continuous murmur is audible. The point of maximal intensity is over the main pulmonary artery, high on the left base, and it radiates cranial to the manubrium and to the right base.[23, 143, 145, 146] Frequently, a systolic murmur is evident over the mitral area, and mitral incompetency does develop with severe left ventricular dilatation. In the cat, the murmur may be heard best more caudoventrally than in the dog and the diastolic component may be less noticeable, particularly if pulmonary hypertension is present. The left ventricular apical impulse is often displaced caudoventrally due to ventricular dilatation. Mucous membranes are pink unless there is severe pulmonary edema from left ventricular failure. Noninvasive studies are diagnostic (Figs. 24–42 through 24–44; see also Fig. 8–16).

ELECTROCARDIOGRAPHY. The ECG usually indicates left atrial enlargement, with widening of the P waves and left ventricular dilatation characterized by a normal frontal axis and increased voltage Q and R waves in craniocaudal leads II, III, and aVF and in the lower left chest leads such as V_2 and V_3 (Fig. 24–43).

RADIOGRAPHY. Chest radiographs document pulmonary overcirculation and left atrial and left ventricular enlargement, and they may show dilation of the main pulmonary artery and descending aorta ("ductus bump") (see Fig. 24–42). It is not uncommon in the cat for the left apex to be displaced into the right hemithorax.

ECHOCARDIOGRAPHY. The echocardiogram substantiates left-sided cardiac enlargement and dilation of the aorta and pulmonary artery. The ventricular shortening fraction is decreased in some dogs, probably due to the severe volume overload imposed on the left ventricle. The ductus can be imaged (see Figs. 8–16; 24–44) in many but not all cases. Doppler echo studies are less ambiguous. Spectral and color-flow Doppler echocardiography show continuous and abnormal retrograde flow in the pulmonary artery (see Fig. 8–16) and mild increases in aortic velocity (generally <2.5 m/s), and they may demonstrate pulmonary and mitral valve insufficiency. Differential diagnosis includes *aortopulmonary window*[162–164] and anomalous systemic-to-pulmonary artery shunt.[165] These are rare conditions, and the aortopulmonary window, a communication between the ascending aorta and pulmonary artery, usually leads to Eisenmenger's physiology. Careful Doppler imaging can usually distinguish a shunt that

enters the PA from the ductus versus one that enters from the ascending aorta.

CARDIAC CATHETERIZATION AND ANGIOCARDIOGRAPHY. These tests (Figs. 9–12*A*, 22–41, 24–22) are not indicated unless intercurrent malformations are strongly suspected and the Doppler echocardiographic study is ambiguous. Associated cardiac defects in dogs with PDA are not common, especially in the smaller canine breeds,[150] and catheterization cannot be justified if noninvasive data support the diagnosis of uncomplicated PDA. Catheterization data may show elevated pulmonary capillary wedge, pulmonary artery, and left ventricular diastolic pressures.[152] Pulmonary and right ventricular pressures are normal to mildly elevated in cases uncomplicated by heart failure or pulmonary vascular disease. An oxygen step-up is recorded in the pulmonary artery. When contrast material is injected into the left ventricle, or preferably the descending aorta, the ductus is evident, and both aorta and pulmo-

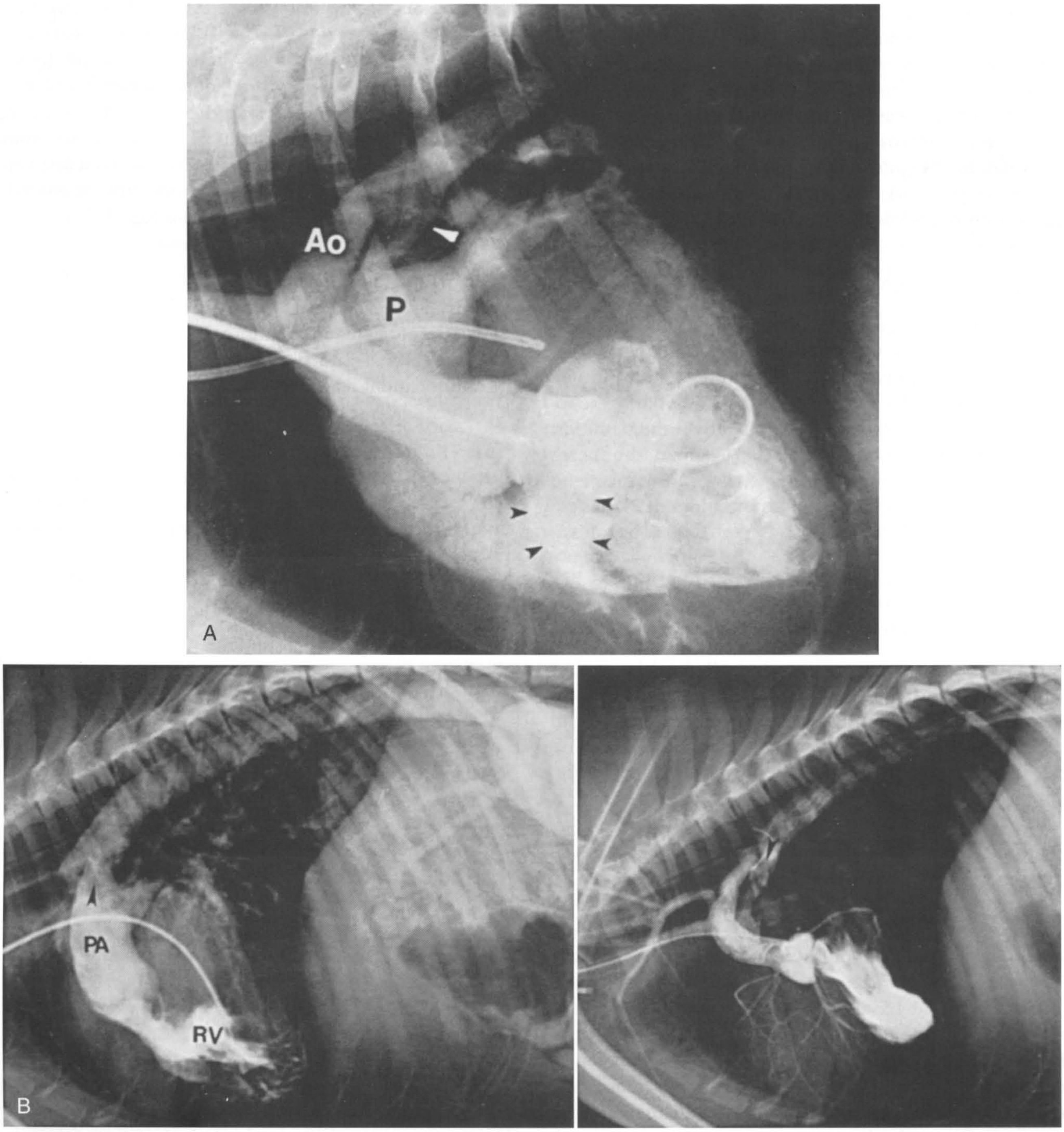


FIGURE 24–41. *See legend on opposite page*

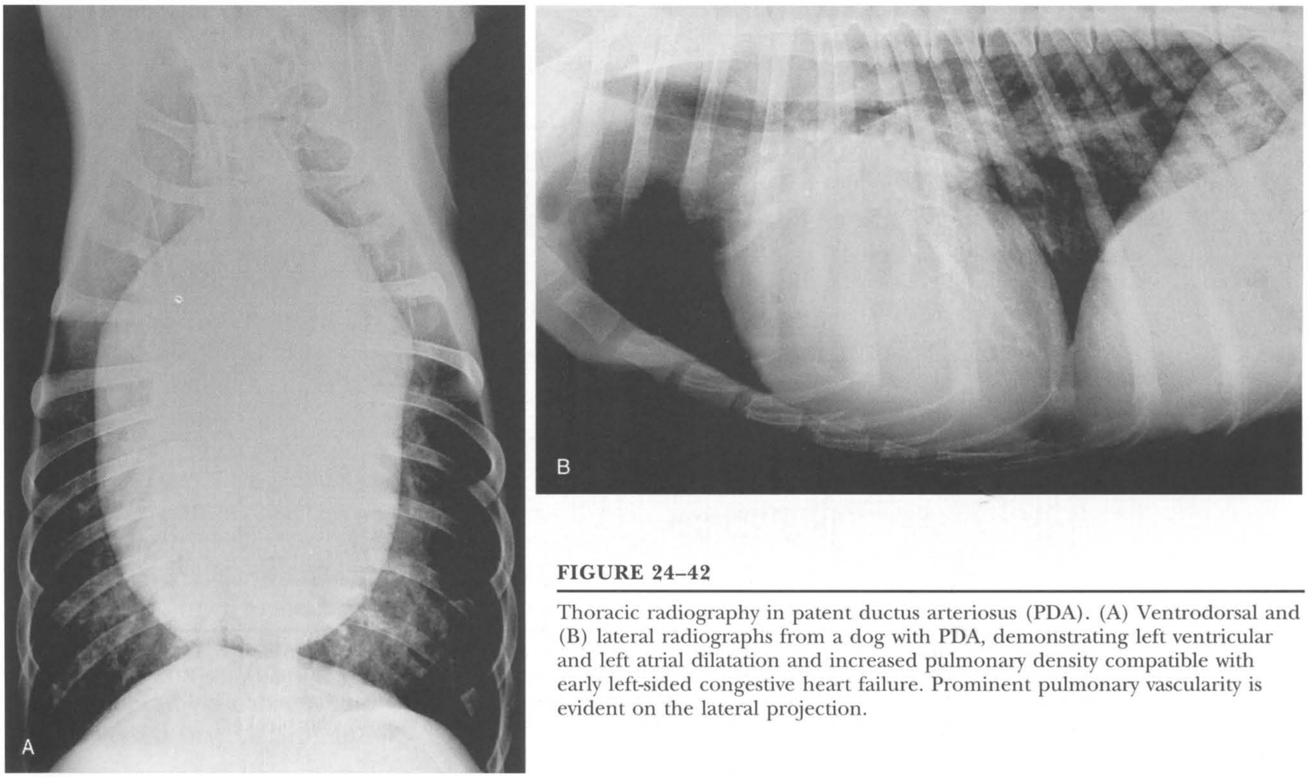


FIGURE 24–42

Thoracic radiography in patent ductus arteriosus (PDA). (A) Ventrodorsal and (B) lateral radiographs from a dog with PDA, demonstrating left ventricular and left atrial dilatation and increased pulmonary density compatible with early left-sided congestive heart failure. Prominent pulmonary vascularity is evident on the lateral projection.

nary artery are opacified. Mitral regurgitation may be present if there is enough left ventricular dilatation, and pulmonic insufficiency may be noted owing to dilation of the pulmonary annulus.

Patent Ductus Arteriosus with Pulmonary Hypertension ("Reversed PDA")

When right-to-left shunting develops as a result of increased pulmonary vascular resistance, a condition called "reversed PDA" is observed.[23, 154]

CLINICAL SIGNS. The symptomatic patient may exhibit shortness of breath, pelvic limb weakness or collapse, seizures, and differential cyanosis (cyanosis of the caudal mucous membranes with pink cranial membranes).[61] Differential cyanosis is readily explained by the location of the right-to-left shunt from the pulmonary artery into the descending aorta (Fig. 24–41). Perfusion of the kidneys with hypoxemic blood leads to secondary polycythemia and hyperviscosity, with the packed cell volume (PCV) often exceeding 65 percent. Metabolic acidosis can develop.

FIGURE 24–41

Angiograms demonstrating patent ductus arteriosus (also see Figure 24–22*A*). (A) Left ventriculogram obtained from a dog with pulmonary hypertension caused by a ventricular septal defect and patent ductus arteriosus. A pigtail catheter is present within the left ventricle, and another catheter is evident within the right atrium. Following injection of contrast into the left ventricle, a stream of dye crosses the ventricular septal defect *(arrowheads)*, opacifies the hypertrophied right ventricular outflow tract and main pulmonary artery *(P)*, and fills the distal pulmonary circulation. Contrast that exits into the aorta *(Ao)* outlines this vessel as well as the ductus arteriosus *(white arrowhead)*, which connects the descending aorta with the dilated main pulmonary artery. (B) Right and left ventricular angiograms obtained from a dog with patent ductus arteriosus, pulmonary hypertension, and bidirectional shunting. The ventriculogram on the left opacifies the right ventricle *(RV)*, the main pulmonary artery *(PA)*, and the large ductus *(arrowhead)*, which subsequently fills the descending aorta and opacifies the kidney. Note that the right ventricular wall is markedly hypertrophied, that there is secondary muscular hypertrophy of the infundibulum, which narrows the right ventricular outflow tract, and that the main pulmonary artery is dilated. The genesis of polycythemia is obvious. Desaturated blood perfuses the caudal portion of the body, including the kidneys, which results in an increase in plasma erythropoietin. The ventriculogram on the right shows a small left ventricle that has been displaced dorsocaudally, prominence of the right coronary circulation, and some degree of left-to-right shunting *(arrowhead)* into the ductus. Note that the contrast in the descending and distal aorta has been diluted by the right-to-left shunt. (From Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, pp 908–909, with permission.)

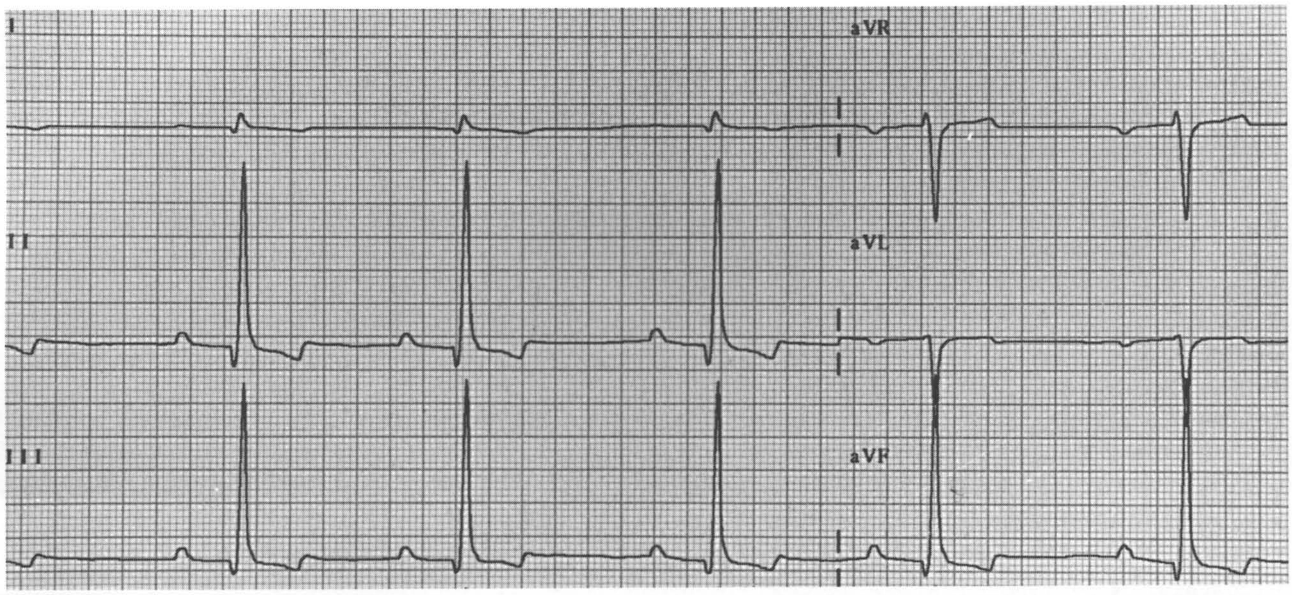


FIGURE 24–43

Electrocardiogram from a dog with patent ductus arteriosus, recorded at 1/2 standard (5 mm = 1 mV; 50 mm/sec). The frontal axis is normal, but Q-waves are prominent (0.5 mV). In lead II, the R-wave amplitude is increased (over 5 mV), indicating left ventricular enlargement. P waves are slightly widened, compatible with left atrial dilatation. There is also first-degree atrioventricular block.

PHYSICAL EXAMINATION. The continuous cardiac murmur is no longer present. An ejection sound, a protosystolic murmur, and a loud or split second heart sound may be evident over the pulmonary artery or left cardiac base. Right ventricular hypertrophy is always expected and can be palpated over the precordium and confirmed by electrocardiography, radiography, and echocardiography.

ELECTROCARDIOGRAPHY. The ECG usually shows evidence of right ventricular hypertrophy (chapter 6).

RADIOGRAPHY. Thoracic radiographs usually demonstrate dilatation of the main pulmonary artery (see Fig. 7–15) and proximal lobar arteries, peripheral hypoperfusion, and a "ductus bump" of the descending aorta. Radiographic signs are sometimes subtle, and the heart may be more misshapen than enlarged (Fig. 24–42).

ECHOCARDIOGRAPHY. The echocardiogram demonstrates right ventricular hypertrophy, a dilated pulmonary artery, and the ductal communication (see Fig. 8–16). Contrast echocardiography, with saline injected in the cephalic vein, will opacify the descending aorta (best observed by imaging the aorta as it courses dorsal to the bladder), but not the left ventricle.

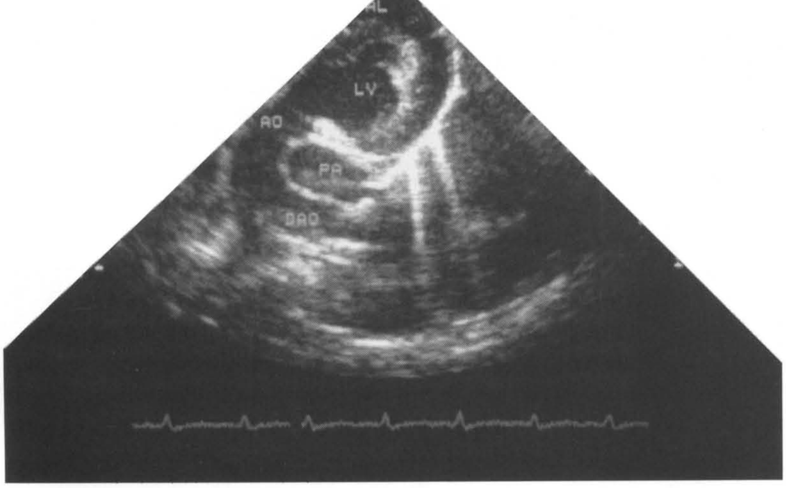


FIGURE 24–44

Subcostal two-dimensional echocardiogram from a dog with patent ductus arteriosus shows the left ventricle *(LV)*, aorta and arch *(Ao)*, descending aorta *(DAO)*, and termination of the ductus into the pulmonary artery *(PA)* *(arrow)*. (Study courtesy of Helio A. DeMorais, DVM.)

CARDIAC CATHETERIZATION. Severe pulmonary hypertension with a corresponding elevation of the right ventricular systolic pressure is recorded at cardiac catheterization, though this test is rarely needed to confirm the diagnosis. Bidirectional shunting is commonly observed during angiography; however, the importance of the right-to-left shunt is emphasized by the thickening of the right ventricular walls, relatively small size of the left atrium and left ventricle, and the oxygen step-down in the descending aorta. The right ventriculogram usually outlines a very large ductus that appears to continue distally as the descending aorta. Some contrast media may flow cranial to the ductus, but most flows caudally. An erroneous diagnosis of pulmonic stenosis can be made from the right ventricular angiogram unless the examiner appreciates that significant hypertrophy develops in response to the pulmonary hypertension. This can cause the right ventricular outflow tract to demonstrate a dynamic, systolic muscular obstruction that abates during diastole. Dilated lobar arteries showing increased distal tortuosity are commonly visualized, and bronchoesophageal collateral vessels may be prominent.

NATURAL HISTORY

With left-to-right shunting PDA, approximately 64 percent of dogs will be dead within 1 year of diagnosis without surgical treatment.[148] Complications of left-to-right PDA include pulmonary edema from left ventricular failure, atrial fibrillation from left atrial enlargement, pulmonary hypertension secondary to left ventricular failure (but *not* vascular disease), and development of mitral regurgitation, presumably from left ventricular dilatation.[152] Some dogs with PDA survive to maturity, and an occasional dog with PDA survives to more than 10 years of age. It is popular to extrapolate from humans and predict that pulmonary hypertension and shunt reversal may develop in mature dogs with PDA. However, we are unaware of a documented case of shunt reversal that has occurred after a dog has attained 6 months of age. Our clinical impression is that cats may develop pulmonary vascular disease and pulmonary hypertension more gradually.

When pulmonary hypertension in the neonate leads to reversed shunting, congestive heart failure is unlikely to develop. However, hypoxemia, polycythemia, and hyperviscosity can incapacitate the dog, and cardiac arrhythmias, seizures, and sudden death may result. Dogs with reversed PDA often live for 2 to 5 years if they are not stressed and if the PCV is controlled below a value of 65 to 68 percent.

CLINICAL MANAGEMENT

Left-to-Right Shunting Patent Ductus Arteriosus

SURGERY. Surgical ligation of the PDA is recommended in all cases of left-to-right shunting PDA diagnosed in dogs less than 2 years of age. When this condition is diagnosed in older pets, a cardiologist should be consulted and the risks and benefits carefully considered. Doppler echocardiography can be used to verify the diagnosis or to rule out concurrent defects and is recommended, especially in larger breeds, because intercurrent defects such as subaortic stenosis seem to be more common. The optimal time for surgery has not been determined, but ductus ligation should be done early, usually between 8 and 16 weeks of age, or sooner if cardiac failure is imminent or myocardial function is obviously reduced on echocardiographic examination. Surgical techniques and results have been described in detail.[141–144, 148, 153, 166–168] When congestive heart failure has developed, the patient is stabilized medically with digoxin and furosemide (see Table 24–3) prior to surgery. Treatment with prostaglandin inhibitors,[149] often used in premature infants to encourage closure of the PDA, is highly unlikely to be successful due to the histologic nature of the lesion (which is characterized by an absence of smooth muscle in the ductal wall) and is not advocated.

Prognosis with surgery is excellent.[143, 148, 166] It is inadvisable to use the dog for breeding. A surgical mortality of greater than 5 to 8 percent should be considered excessive in uncomplicated cases. Ductal recanalization has been reported to be uncommon, occurring in 2 percent or less of the cases[147]; however, recent experience with Doppler echocardiography indicates that persistent ductal flow is very common for weeks after surgery, and perhaps longer. When no PDA murmur is audible postoperatively, it is doubtful that identifying residual flow by Doppler is of clinical significance. However, when an audible murmur is identified, religation or coil embolization should be considered. Recanalization is particularly likely to develop when there is infection at the surgical site. Postoperative fever and diffuse pulmonary infiltrates, generally developing within 2 weeks of surgery, usually indicate infection at the surgical site and hematogenous pneumonia (Fig. 24–45).

TRANSCATHETER OCCLUSION. An alternative to surgical correction of the ductus is coil embolization via transcatheter delivery of a Gianturco coil or another specialized device or occluder.[169, 169a, 169b] This technique has been accomplished successfully in a number of dogs (Fig. 24–46). Potential complications include pulmonary embolism due to placement of a coil of insufficient diameter or poor coil placement.

PROGNOSIS. The long-term prognosis for dogs and cats treated surgically appears to be good. Detailed follow-up studies have not been reported, but most pets are clinically normal following surgery, and overall cardiac size becomes normal, though the heart and great vessels continue to be misshapen in outline.[150]

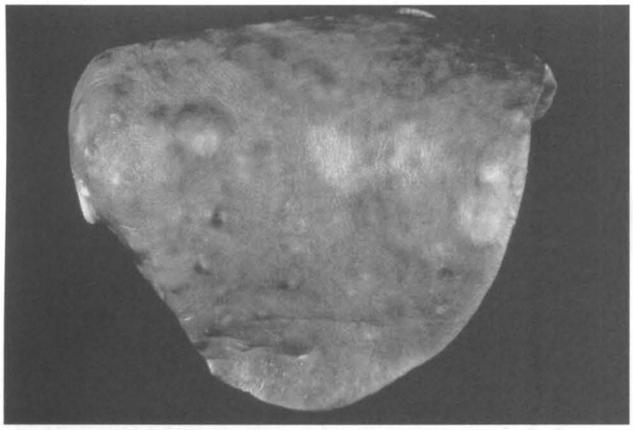


FIGURE 24–45

Postoperative pulmonary complications can be caused by infection of the suture/ligation site in dogs with patent ductus arteriosus. In addition to pulmonary complications and the risk of sepsis, infection at the surgical site may promote recanalization of a ductal or periductal channel. Lung from a dog demonstrates multifocal pulmonary abscesses.

Soft left- or right-sided systolic murmurs are commonly detected immediately following ductus ligation but are generally absent at the time of suture removal.[145] Persistent systolic murmurs are likely to indicate mitral regurgitation or an undetected lesion such as mitral valve dysplasia, ventricular septal defect, or subaortic stenosis. Myocardial function, as assessed by echocardiography, may be decreased following surgery, and this likely represents a cardiomyopathy of volume overload. The progression or regression of this has not been investigated. When atrial fibrillation or advanced congestive heart failure is present in PDA, the prognosis is guarded to poor, and these patients are poor anesthetic risks.[152]

"Reversed" Patent Ductus Arteriosus

Treatment of *reversed PDA* with secondary polycythemia consists of enforced rest, limitation of exercise, avoidance of stress, and maintenance of the PCV below 65 percent. Excessive bleeding is discouraged since the oxygen content of arterial blood may be diminished, leading to tissue hypoxia. Fluid volume should be maintained during phlebotomy by infusing crystalloid solutions.

LESIONS CAUSING PULMONARY-TO-SYSTEMIC SHUNTING (CYANOTIC HEART DISEASE)

A number of congenital heart diseases characterized by pulmonary-to-systemic (right-to-left) shunting lead to the clinical sign of cyanosis (see Table 24–2). Each has the potential to cause substantial systemic arterial desaturation and clinical signs related to tissue hypoxia and polycythemia. Whereas tetralogy of Fallot (see Figs. 24–47 through 24–50) is the most common right-to-left shunt in small animals,[24–26, 60, 170–179] other causes of cyanotic congenital heart disease occur. These conditions have in common a number of pathophysiologic abnormalities.[115]

PATHOPHYSIOLOGY OF RIGHT-TO-LEFT SHUNTING

In order for desaturated venous blood to shunt into the systemic arteries, there must be mixing of blood between the pulmonary and systemic circulations. This generally involves a septal defect or aorticopulmonary communication and some lesion that raises pressures on the right side of the circulation; alternatively (and rarely), there can be transposition of the great vessels relative to the venous return, or a single functional

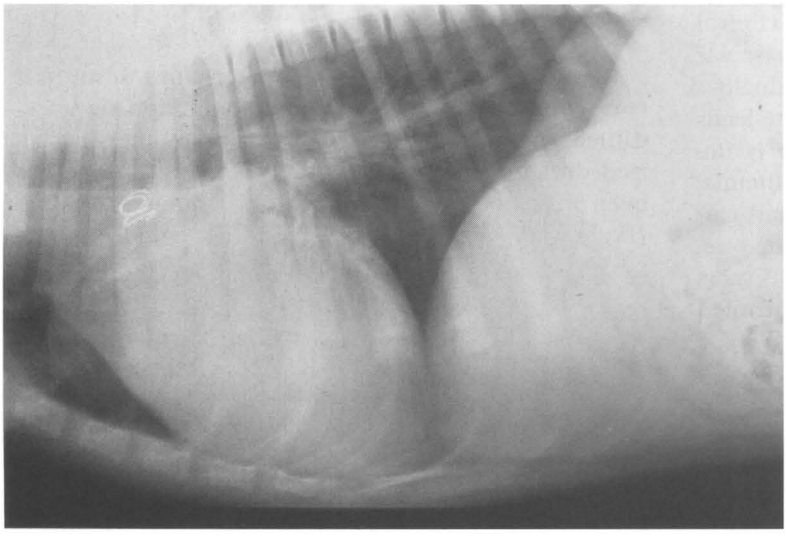


FIGURE 24–46

Thrombogenic Gianturco coil occluding a patent ductus arteriosus in a Gordon setter puppy. The ductus had been partially ligated at surgery and coil-related thrombosis resulted in complete clinical closure of the shunt.

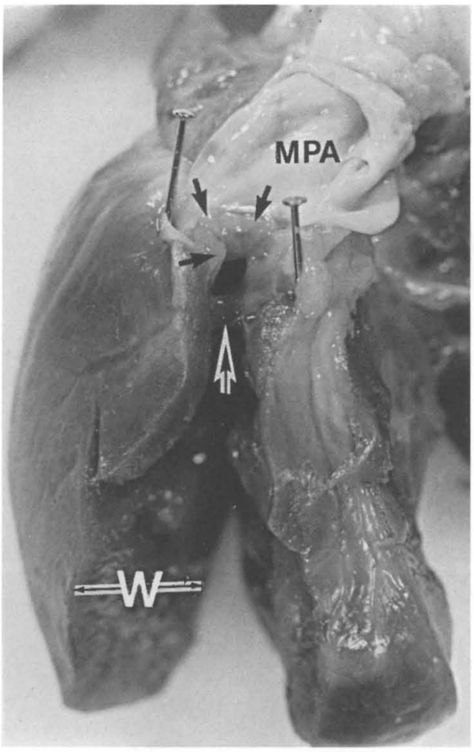


FIGURE 24–47

Heart from a 5-month-old male domestic short-hair cat with tetralogy of Fallot. The right ventricular outflow tract and pulmonic valve are exposed. Hypertrophy of the infundibular portion of the right ventricular outlet is evident along with pulmonary valve stenosis (dysplasia) is indicated by three black arrows. The right ventricular outflow tract is very narrowed *(lower arrow)*. The right ventricular wall *(W)* is severely hypertrophied. *MPA*, main pulmonary artery. (Courtesy of Dr. Philip Fox.)

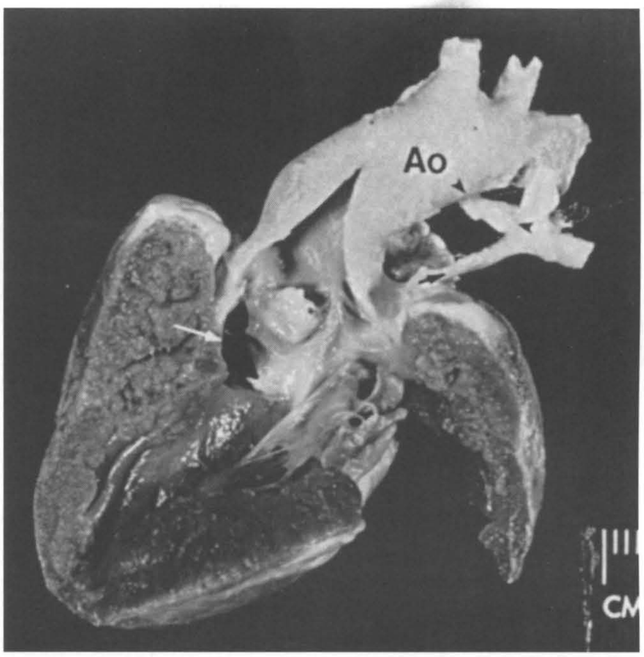


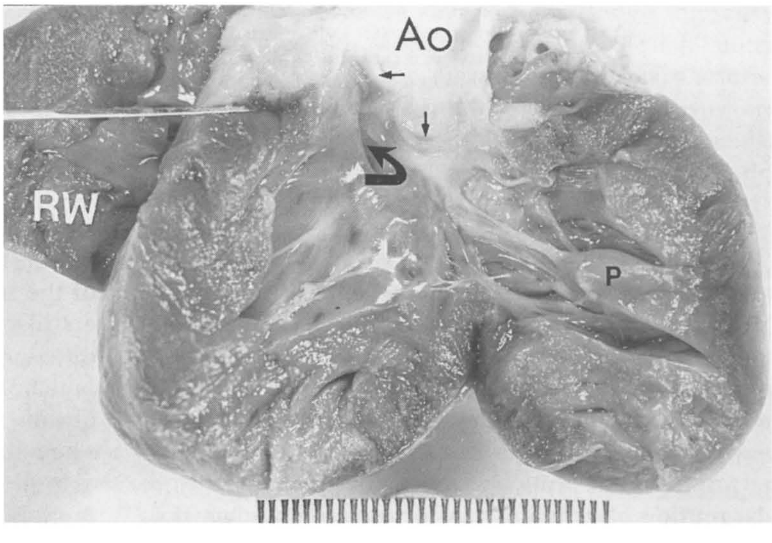
FIGURE 24–49

Gross dissection of a feline heart with tetralogy of Fallot and pulmonary artery atresia (pseudotruncus arteriosus). The left ventricle has been opened to expose the large ventricular septal defect *(white arrow)*, the hypoplastic pulmonary artery *(black arrow)*, and dilated aorta *(Ao)*. Pulmonary flow was through the ductus arteriosus, the origin and termination of which are shown by arrowheads. The lobar pulmonary arteries were patent, but almost no blood was found in the main pulmonary artery. (From Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 935, with permission.)

ventricle that serves both circulations. A defect between the atrial, ventricular, or aorticopulmonary septa or a PDA provides the potential conduit for right-to-left shunting in most cases. However, this condition will not develop unless there is an obstruction to blood flow on the right side of the circulation. Tricuspid stenosis (or atresia) and pulmonic stenosis (or atresia) are examples of obstructive right-sided cardiac lesions. Pulmonary vascular disease is another cause of high right-sided pressures that can lead to right-to-left shunting. This concept was introduced previously (see Reversed Patent Ductus Arteriosus) and is discussed later (Eisenmenger's Physiology).

FIGURE 24–48

Left ventricle and aortic root of the cat in Figure 24–47. A large ventricular septal defect *(curved arrow)* is present. The aortic root *(Ao)* and aortic semilunar valves *(small arrows)* are illustrated. There is severe hypertrophy of the right ventricular wall *(RW)*. Mitral valve malformation and endocardial fibrosis are also present. *P*, papillary muscle. (From Liu SK. Cardiovascular pathology. *In* Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, pp 637–660, with permission.)



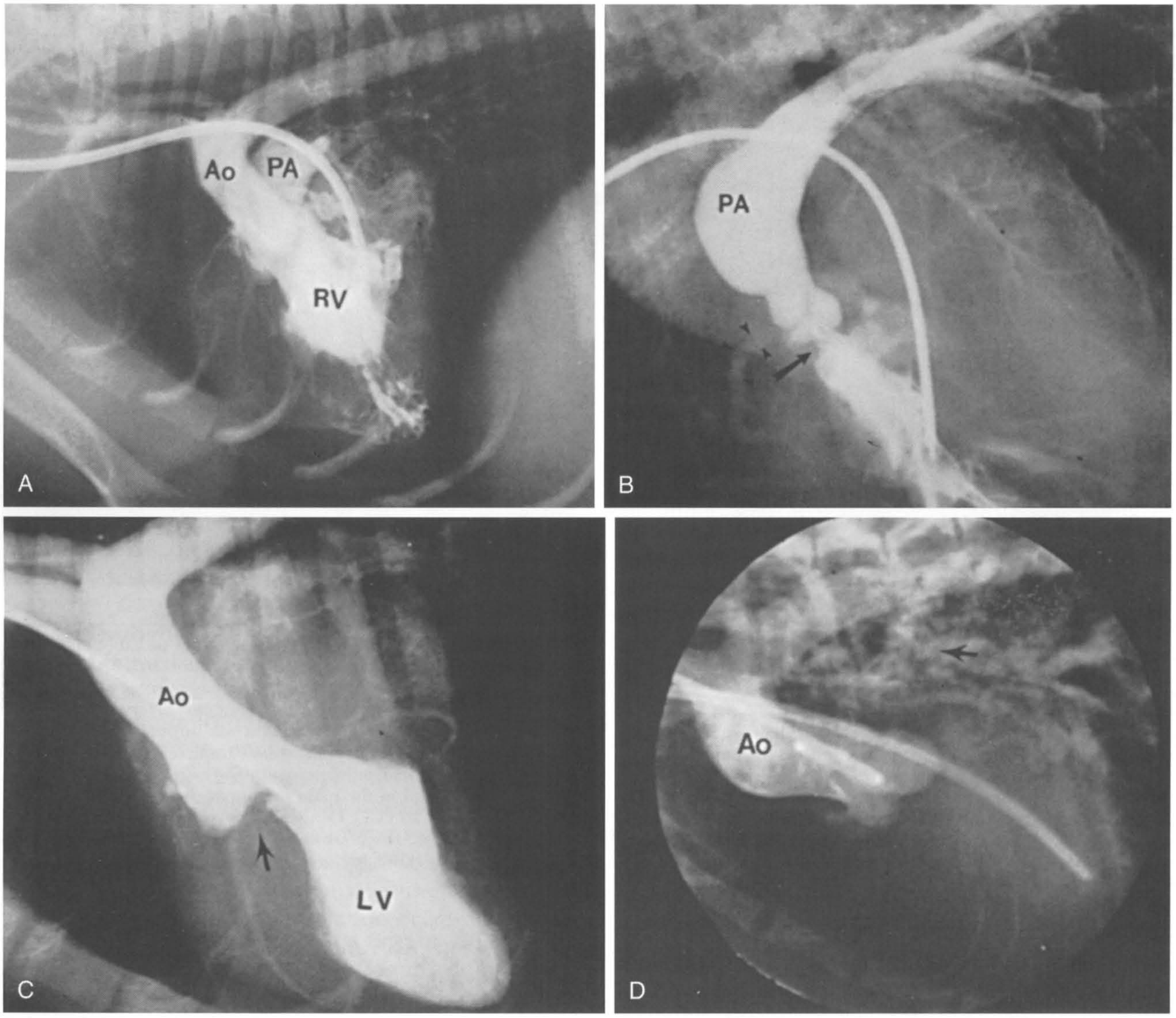


FIGURE 24–50

Angiocardiograms from animals with tetralogy of Fallot. (A) A right ventricular *(RV)* injection documents simultaneous opacification of both the pulmonary artery *(PA)* and the aorta *(Ao)* in this dog. The right ventricular wall is hypertrophied. (B) A right ventriculogram from a dog documents a subvalvular pulmonic stenosis *(arrow)* and normally formed, but relatively small, pulmonary valve sinuses above the arrow. There is mild poststenotic dilation of the main pulmonary artery and slight opacification of the ascending aorta cranial to the pulmonary artery. A dilated right coronary artery is shown *(arrowheads)*. (C) Left ventricular injection showing overriding of the aorta *(arrow)*. (D) Aortic injection in a cat with tetralogy of Fallot. The aorta is slightly widened, and there is marked increase in collateral circulation via the bronchoesophageal system *(arrow)*. The tortuous nature of these vessels is typical of collateral flow in right-to-left cardiac shunting. (From Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p. 938, with permission.)

The degree of right-to-left shunting varies with the systemic vascular resistance or the ratio of pulmonary (or right-sided)-to-systemic resistance. Exercise may promote systemic vasodilation, increase the pulmonary-systemic resistance ratio, and increase the right-to-left shunt. Tachycardia or elevated sympathetic tone may cause difficulties in cases of right ventricular hypertrophy, because any dynamic component of ventricular outflow obstruction may increase, pulmonary flow diminish, and right-to-left shunting worsen. This is one of the suggested reasons for using β-adrenergic blockers like propranolol in some forms of cyanotic heart disease.[180, 181] Anemia or even relative anemia (normal hematocrit in a hypoxemic patient) can result in a decline in the ratio of systemic-to-pulmonary resistance when the pulmonary resistance is a fixed lesion such as pulmonic valve stenosis.[182] Therefore, phlebotomy in cyanotic patients not only decreases oxygen content

per deciliter blood but also decreases systemic vascular resistance, increasing the arterial hypoxemia. The quantitative impact on systemic-to-pulmonary resistance of reducing hematocrit in animals with pulmonary hypertension has not been reported.

Right-to-left shunting leads to compensatory increases in blood flow to the lung via the bronchial arteries. These tortuous systemic collateral vessels are easily recognized with angiography (see Fig. 24–50*D*) ventral to the descending aorta. Blood from these vessels may return via pulmonary veins and increase venous admixture. Although uncommon, it is possible for these vessels to rupture, leading to hemoptysis.

Systemic hypoxemia can be detected by measuring an arterial blood gas obtained while the animal breathes room air. Increasing the inspired oxygen concentration to 100% neither significantly improves the hypoxemia nor the cyanosis in most cases of right-to-left shunting. Clinical signs of cyanotic heart disease are a result of tissue hypoxia and include stunting, weakness, anxiety, syncope, and seizures.[59, 60, 115, 126, 180, 182, 183] Since systemic hypoxemia increases plasma erythropoietin concentrations, secondary polycythemia develops in cyanotic heart disease. When the PCV exceeds the 65 to 68 percent range, hyperviscosity can predispose to thrombosis and microvascular complications. Metabolic acidosis is another potential complication of protracted hypoxemia.[14]

Paradoxic embolization or a systemic venous–to–systemic arterial embolus is another potential concern in right-to-left shunting. Normally, the pulmonary vasculature filters systemic venous emboli before they can reach the left side of the circulation. With reversed shunting, the possibility of coronary, cerebral, or other systemic emboli must always be considered, particularly when venipuncture or intravenous catheters are used. Air, thrombi, or bacteria may gain access to vital organs by this mechanism.

TETRALOGY OF FALLOT

Tetralogy of Fallot is a genetically transmitted disorder in some breeds, propagated as a single major gene defect interfering with myocardial growth.[25] This malformation has been widely studied in the keeshond breed in which a spectrum of lesions is described, ranging from subclinical to clinically complicated.[9, 24–26]

DEVELOPMENTAL ANATOMY

It is hypothesized that tetralogy of Fallot results from conotruncal system malformation, the swellings responsible for partitioning of the fetal truncus arteriosus into the aorta and pulmonary artery and the fetal conus arteriosus into right and left ventricular outflow tracts. When the conotruncal septum fails to develop completely, there is often a VSD with malalignment between the ventral and most dorsal components of the ventricular septum, leading to a dextropositioned and overriding aorta.[118]

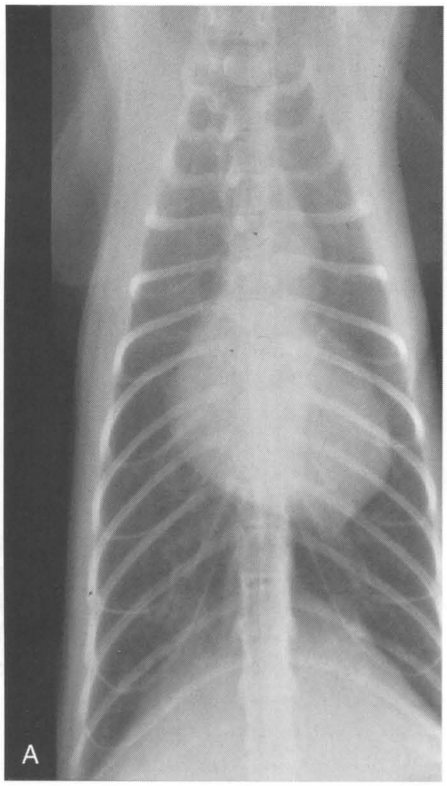
LESIONS

Components of the tetralogy are (1) right ventricular outflow obstruction (pulmonic stenosis), (2) secondary right ventricular hypertrophy, (3) a subaortic ventricular septal defect, and (4) dextropositioned or overriding aorta (Figs. 24–47 through 24–53). When pulmonary atresia occurs owing to grossly unequal partitioning of the truncus, the term "pseudotruncus arteriosus" has been used (Fig. 24–49).

GROSS MORPHOLOGY. Patterson and colleagues graded the conotruncal defects pathologically as follows: grade 1—persistence of the conus septum fusion line, aneurysm of the ventricular septum, and absence of the papillary muscle of the conus (representing subclinical malformations); grade 2—pulmonic stenosis or infundibular ventricular septal defect plus the grade 1 lesions; and grade 3—tetralogy of Fallot: pulmonic stenosis, infundibular (outlet) ventricular septal defect, and dextropositioned aorta (with secondary right ventricular hypertrophy), plus grade 1 lesions. Other lesions found in some dogs included dilated and tortuous ascending aorta, pulmonary atresia, hypoplasia of the supraventricular crest, and anomalies of the aortic arch system. More detailed descriptions can be found in related literature.[24–26]

PATHOPHYSIOLOGY

As with other right-to-left shunts, the essential components are the increased right-sided resistance and pressure and the communication between pulmonary and systemic circulations (Fig. 24–50). Owing to the high resistance RV outlet and elevated right ventricular pressure, desaturated blood shunts through the septal defect to mix with blood coming from the left ventricle.[115, 170, 171] Due to the decreased pulmonary arterial flow, the left atrium and left ventricular cavity are small. The significant contribution of right ventricular blood to systemic blood flow causes hypoxemia, decreased hemoglobin oxygen saturation (O_2 saturation), cyanosis, and secondary polycythemia. A cardiac murmur is generated from high-velocity flow across the pulmonic stenosis or, less often, from shunting across the VSD. Systemic collateral circulation increases via the bronchial arterial system, increasing venous admixture and hypoxemia. Right ventricular hypertrophy develops in response to pulmonic stenosis. Other aspects of clinical pathophysiology have been previously described (see Pathophysiology of Right-to-Left Shunting). In cases of pulmonary atresia, pulmonary blood



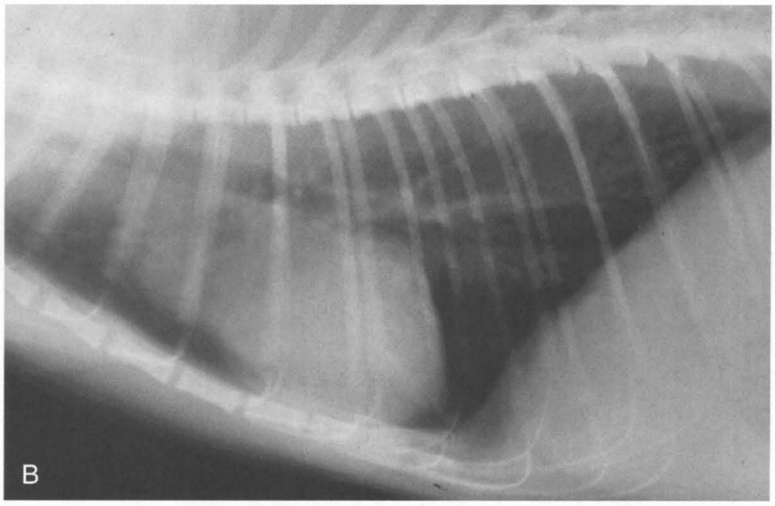


FIGURE 24–51

(A) Ventrodorsal (VD) and (B) right lateral thoracic radiographs from a cat with tetralogy of Fallot and pulmonary atresia (pseudotruncus arteriosus). The right side of the heart is enlarged, resulting in apex displacement to the left on the VD view (A). The ascending aorta is dilated because of unequal partitioning of the truncus arteriosus, and it is malpositioned, resulting in a bulge in the cranial border of the heart on the lateral view (B). The left auricle is small, and pulmonary vascularity is reduced owing to decreased pulmonary blood flow.

flow must be derived from either a persistently patent ductus arteriosus or from bronchial arteries.[14, 160]

CLINICAL FINDINGS

SIGNALMENT. Tetralogy of Fallot is common in the keeshond, English bulldog, and some families of other breeds.[34] It is also recognized in the cat.[172–178]

CLINICAL SIGNS. Presenting signs include failure to grow, cyanosis, shortness of breath, exercise intolerance, weakness, syncope, and seizures.

PHYSICAL EXAMINATION. The ejection murmur of pulmonic stenosis is the most common auscultatory abnormality. Detection of a murmur over the right hemithorax is not uncommon and may indicate radiation of the pulmonic stenosis (PS) or, less likely, flow across

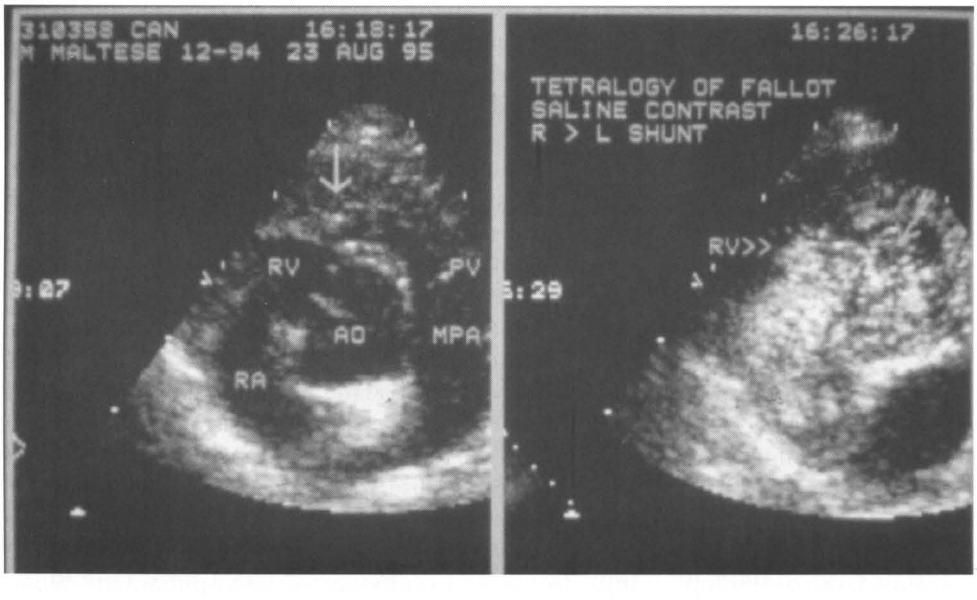


FIGURE 24–52

Two-dimensional echocardiograms from a dog with tetralogy of Fallot. *Left panel*: A short-axis image across the base of the heart shows infundibular obstruction *(arrow)* of the right ventricle and a large septal defect communicating between the right ventricle *(RV)* and the root of the aorta *(AO)*. *RA*, right atrium; *MPA*, main pulmonary artery; *PV*, pulmonary valve. *Right panel*: Contrast two-dimensional echocardiogram following injection of agitated saline into a cephalic vein. Both the right side of the heart and the aortic root *(arrow)* are opacified, thereby demonstrating the right-to-left shunt. *RV*, right ventricle.

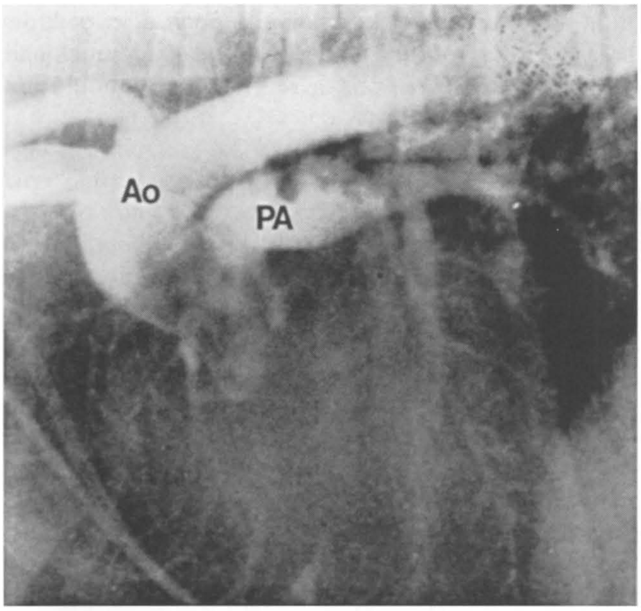


FIGURE 24–53

Successful systemic-to-pulmonary shunt used to palliate the tetralogy of Fallot. Following injection of contrast into the aorta, the pulmonary artery is also opacified. A filling defect (above the *A* in *PA)* is a result of surgical scarring. *Ao*, aorta. (From Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 939, with permission.)

the septal defect and in the ascending aorta. Some dogs have no obvious murmur related to pulmonary atresia and/or polycythemia with hyperviscosity (which decreases turbulence) and ejection across a large, nonrestrictive VSD. Cyanosis is typical, but acyanotic cases are not uncommon. Exercise or excitement may induce cyanosis by accentuating right-to-left shunting. Affected animals often gasp when stressed, and pulmonary crackles are commonly heard though they do not represent edema and their genesis is not understood. Arterial pO_2 and pCO_2 are decreased. These animals may develop adverse reactions (particularly bradycardia) to sedatives and tranquilizers, and they may not improve appreciably following administration of supplemental oxygen. Most cases are polycythemic, but the hemoglobin concentration must be compared with age-matched normal animals.[60]

RADIOGRAPHY. Thoracic radiographs usually show a normal-sized heart with rounding of the right ventricular border (Fig. 24–51). The main pulmonary artery is not enlarged in contrast to the usual case of PS with intact ventricular septum. Pulmonary circulation is diminished, and the left auricle may be inconspicuous due to decreased venous return.

ECHOCARDIOGRAPHY. The two-dimensional echocardiogram reveals right ventricular hypertrophy, small left chamber dimensions, the large subaortic VSD, and right ventricular outflow obstruction. Echo contrast (or Doppler echo) studies (Fig. 24–52) document right-to-left shunting at the ventricular outflow level.[184]

ELECTROCARDIOGRAPHY. The ECG usually exhibits a right axis deviation. However, a left or cranial axis may be found in some cats.[172]

CARDIAC CATHETERIZATION. Catheterization demonstrates virtual equilibration of left and right ventricular systolic pressures in most cases, compatible with an unrestrictive VSD.[60] An oxygen step-down is recorded at the left ventricular outflow level, and the aortic blood is relatively desaturated. Angiocardiography reveals right ventricular hypertrophy, PS with minimal poststenotic dilatation, a large subaortic VSD, a small, dorsally displaced left ventricle, a widened ascending aorta, and prominent bronchial circulation (Figs. 9–12*F*, 24–50). Either valvular or subvalvular PS, or both, may be found. Bidirectional shunting across the VSD is common in the anesthetized animal. Anticoagulation therapy (e.g., heparin) should be considered to prevent cerebral thromboembolism during and immediately after cardiac catheterization. Care must be taken to avoid air emboli.

NATURAL HISTORY

Generally, pets tolerate the defect for years provided pulmonary blood flow is maintained and hyperviscosity is controlled.[60, 176] Sudden death is common, related to complications of hypoxia, hyperviscosity, or cardiac arrhythmia. Unlike the case in pulmonic stenosis with intact ventricular septum, CHF is extremely uncommon.

CLINICAL MANAGEMENT

Both medical and surgical therapies can be employed in the management of tetralogy of Fallot.

Surgery

Definitive correction of the defect (closing the VSD and removing or bypassing the PS) can be done under cardiopulmonary bypass, but such surgery is rarely performed in animals.[179] The right ventricular outflow tract obstruction should not be relieved surgically if the VSD cannot be closed, because marked left-to-right shunting with subsequent left ventricular failure may develop.[60] Surgical palliation by creation of a systemic-to-pulmonary shunt can be rewarding (Fig. 24–53).[60, 178] Subclavian to pulmonary artery (Blalock-Taussig), ascending aorta to pulmonary artery (Potts), and aorta to right pulmonary artery (Waterston-Cooley) connections have been made in dogs and cats. By increasing pulmonary venous return to the left heart,

there is a greater contribution of oxygenated blood to the systemic circulation. The size of the shunt must be controlled to prevent overloading of the diminutive left ventricle and subsequent pulmonary edema. The extent to which these shunts remain patent postoperatively has not been reported, but the authors have observed patency in some cases for up to 4 years.

Medical Therapy

Adjunctive therapy includes phlebotomy to control the PCV below 65 to 68 percent (in the normally hydrated patient), which appears satisfactory for most cases. Excessive bleeding should not take place, and the blood volume should be maintained with crystalloid fluids to preserve cardiac output and tissue oxygen delivery.[182] Some children with tetralogy of Fallot benefit from β-blockade with propranolol; however, controlled studies of the clinical efficacy of this treatment in animals have not been reported.[180, 181] Severe hypoxic spells should be treated with cage rest, oxygen, and sodium bicarbonate (if metabolic acidosis is evident). Drugs with dominant systemic vasodilating properties and vigorous exercise should be avoided.

EISENMENGER'S PHYSIOLOGY

The term "Eisenmenger's physiology," or "reaction," describes right-to-left shunting consequent to pulmonary vascular disease. This condition usually develops early in life and leads to reversal of a previously left-to-right shunt.[14, 126, 133, 185]

PATHOPHYSIOLOGY

High flow rates or direct transmission of systemic pressures into the pulmonary arterial system is important for development of this syndrome,[130, 131] although many details of etiopathogenesis are incompletely understood. There is an association between large bore defects and the development of pulmonary vascular disease. Reversed shunting has been observed with PDA, aorticopulmonary communication, ventricular septal defect, and atrial septal defect.[23, 30, 114, 126, 128, 133, 154] Moreover, Eisenmenger's physiology almost always develops before 6 months of age in small animals.

The systemic circulation acts as a safety "pop-off" valve for the pulmonary hypertension in this condition, but this leads to the right-to-left shunt and resultant clinical signs. The left atrium and left ventricle are small owing to decreased pulmonary venous return, and bronchial collateral vessels are increased in size. These lesions explain why surgical shunt closure cannot be undertaken. Shunt closure would preclude access of right ventricular blood to the systemic circulation, markedly increase right ventricular afterload, decrease cardiac output, and usually lead to shock and death. For these reasons, a reversed PDA should not be ligated.

LESIONS

GROSS MORPHOLOGY. An atrial septal defect,[30, 114, 128] ventricular septal defect,[30, 126, 128] aorticopulmonary septal defect,[162-164] PDA,[23, 154] or some combination of these defects is present. Aside from the presence of the large-caliber shunt, the most important anatomic changes are microscopic lesions of the muscular and small pulmonary arteries.

HISTOLOGIC FEATURES. Pulmonary vascular lesions observed in dogs and cats with Eisenmenger's physiology are similar to those of humans.[14, 133, 185] Intimal thickening, medial hypertrophy, and plexiform lesions are the salient abnormalities in most cases. The plexiform lesion is considered irreversible; consequently, neither medical therapy nor closure of the shunt will effectively improve the condition once these lesions have developed. The right ventricle becomes hypertrophied because it must eject against a tremendous pulmonary vascular resistance.

CLINICAL FINDINGS

PHYSICAL EXAMINATION. Clinical features of pulmonary-to-systemic shunting in Eisenmenger's physiology tend to be similar to those of the tetralogy of Fallot, regardless of the underlying lesions, with a few notable differences. An important auscultatory finding of Eisenmenger's syndrome is the presence of a loud pulmonic component of the second heart sound related to pulmonary hypertension. In some dogs, the second sound is audibly split. These may be the only auscultable abnormalities and are lacking in tetralogy of Fallot. An ejection sound with a soft, short, systolic murmur also may be evident at the base of the left side of the heart in dogs with Eisenmenger's physiology. Diastolic murmurs of pulmonic insufficiency are rare.

NONINVASIVE TESTING. Eisenmenger's physiology is characterized by right ventricular hypertrophy. This is usually evident on echocardiograms, ECG, and the thoracic radiograph.

RADIOGRAPHY. Marked cardiomegaly is atypical of most cyanotic cardiac conditions, and the heart often does not appear enlarged on survey films. As a general rule, the lungs appear underperfused, and the main pulmonary artery and proximal lobar arteries are dilated when Eisenmenger's syndrome is the basis for reversed shunting. In contrast, the main pulmonary artery is not prominent in cases of cyanosis due to

tetralogy of Fallot, pulmonary atresia, or tricuspid atresia.

ECHOCARDIOGRAPHY. The echocardiogram is usually diagnostic in cases of Eisenmenger's physiology. Most large defects can be easily visualized, the right ventricular inflow and outflow tracts can be evaluated, and the site of right-to-left shunting identified through echocontrast or Doppler studies. Of note is the markedly dilated right ventricular outflow tract and pulmonary artery evident with Eisenmenger's physiology. An atretic, hypoplastic, or stenotic right ventricular outflow tract is generally incompatible with the diagnosis of Eisenmenger's physiology. With reversed PDA, in which imaging of the ductus may be limited by surrounding lung, a peripheral venous injection of agitated saline will eventually opacify the descending aorta, which is easily visualized dorsal to the bladder. Detailed ultrasound studies often render cardiac catheterization unnecessary, unless surgery is contemplated and pulmonary hypertension (as opposed to pulmonic stenosis) cannot be otherwise ruled out. If pulmonic valve insufficiency is observed by Doppler echocardiography, a regurgitant jet peak velocity of less than 2.5 m/s argues against a diagnosis of pulmonary hypertension.

CARDIAC CATHETERIZATION. This can demonstrate pulmonary hypertension, outline anatomic defects, and assess pulmonary artery size and degree of shunting. Angiocardiograms in cyanotic heart disease can be very confusing. It is helpful to include a vena caval and possibly, a right atrial injection of contrast material in the angiographic series. The operator must also watch for abnormal catheter positions as a clue to large septal defects and vessel transpositions. Aortic injections demonstrate prominent collateral bronchoesophageal vessels (Fig. 24–50*D*).

CLINICAL MANAGEMENT

Management of the cyanotic patient requires that the clinician know the cause, the pulmonary artery pressure and resistance, and the reason for right-to-left shunting. It is essential to determine whether or not pulmonary hypertension is present prior to any cardiac or vascular surgery in a patient with cyanotic heart disease. When pulmonary vascular resistance is normal, as with tetralogy of Fallot or pulmonary atresia, then pulmonary flow can be augmented and systemic hypoxemia improved by creation of a shunt between a systemic and a pulmonary artery. Conversely, the patient with Eisenmenger's physiology has irreversible pulmonary vascular disease. The high vascular resistance of this condition negates the benefit of surgery. Otherwise, the general management is similar to that described previously for tetralogy of Fallot. It involves controlling the PCV and preventing signs of hyperviscosity.

OTHER CAUSES OF CYANOTIC CONGENITAL HEART DISEASE

TRICUSPID VALVE DYSPLASIA

Tricuspid valve dysplasia can cause cyanosis when associated with severe valve stenosis (Fig. 24–54), atresia, or regurgitation, since elevated right atrial pressure may generate right-to-left shunting through an ASD or patent foramen ovale.[186] The right ventricle is hypoplastic or atretic in tricuspid stenosis unless there is an associated VSD, in which case there may be a functional remnant of the ventricular outflow tract.

DOUBLE-OUTLET RIGHT VENTRICLE

Double-outlet right ventricle, in which both great vessels exit from the right ventricle, has been reported in dogs and cats.[187, 188] A malalignment type of VSD provides the left ventricle an avenue for outflow into the great vessels. Pulmonary overcirculation is present unless there is pulmonic stenosis or pulmonary hypertension develops. Cyanosis is likely based on the origin of the aorta and is most severe if there is PS or pulmonary hypertension.

D-TRANSPOSITION OF THE GREAT ARTERIES

In dextrotransposition of the great arteries, the aorta originates from the right ventricle and the pulmonary trunk from the left ventricle.[189] Since two completely independent circulations exist and the systemic arteries never receive oxygenated blood, the pure form of this lesion is lethal. Survival of an animal with D-transposition depends on the presence (or production) of shunts between the two circulations to allow for mixing of blood to prevent fatal hypoxemia. If the shunts are large, then pulmonary-to-systemic flow may be great. These defects are complex, generally lethal, and probably underdiagnosed in the neonatal period.

TRUNCUS ARTERIOSUS

Persistent truncus arteriosus represents a failure of partitioning of the fetal truncus, such that a large VSD allows blood flow between the ventricles and a single large vessel originates above the VSD.[190] Classification depends on the location and number of pulmonary arteries that arise directly from the truncus.[14] Ventricular blood mixes within the common artery prior to distribution to the body and pulmonary vessels. The clinical signs will depend in part on the ratio of pulmonary-to-systemic blood flow.

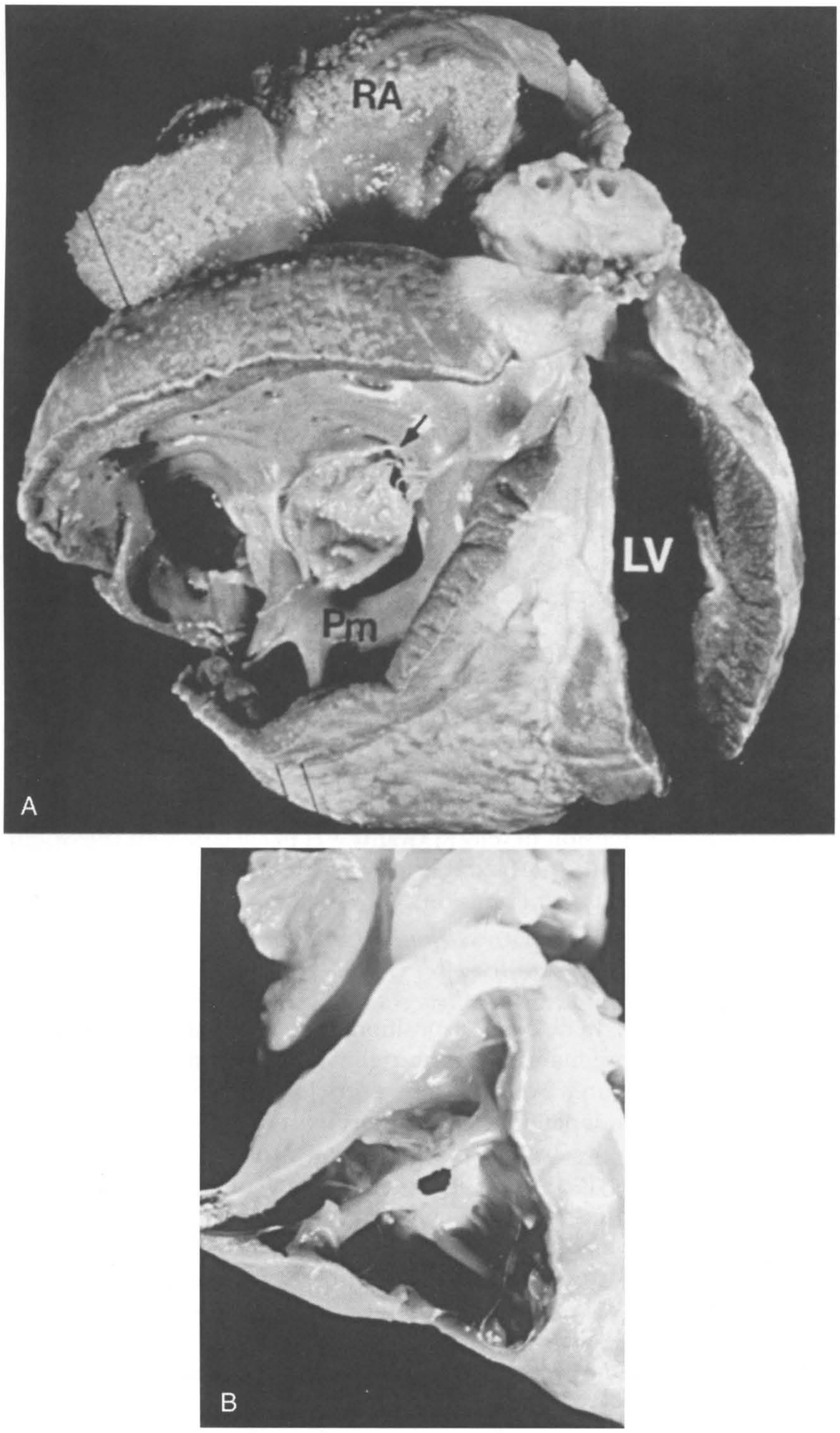


FIGURE 24–54

Tricuspid valve malformation. (A) Postmortem specimen from a dog with tricuspid valve dysplasia. The right atrium *(RA)* is markedly dilated as a result of tricuspid regurgitation. The tricuspid valve itself is grossly malformed, with short chordae tendineae *(arrow)*. malformation of the valve leaflets and cusps, and abnormalities of the papillary muscles *(Pm)*, characterized by a single large papillary muscle instead of the usual three to four smaller muscles. (B) Postmortem examination of a congenitally stenotic tricuspid valve from a cat with right-sided congestive heart failure. The narrowed orifice is obvious when viewed from the ventricular perspective. (From Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 930, with permission.)

Pulmonary atresia with ventricular septal defect, essentially the exaggerated form of tetralogy of Fallot, appears quite similar to truncus arteriosus, except that the pulmonary circulation is derived from either a patent ductus arteriosus or the bronchial arterial circulation. This lesion is sometimes termed "pseudotruncus arteriosus" (Fig. 24–49). Angiocardiography may be required to distinguish these two conditions.

DYSPLASIA OF THE ATRIOVENTRICULAR VALVES

Dysplasia of the mitral and tricuspid valves has been reported in both cats and dogs (Figs. 24–54, 24–55).[2, 8, 41, 186, 191–198] Many have involvement of both valves.

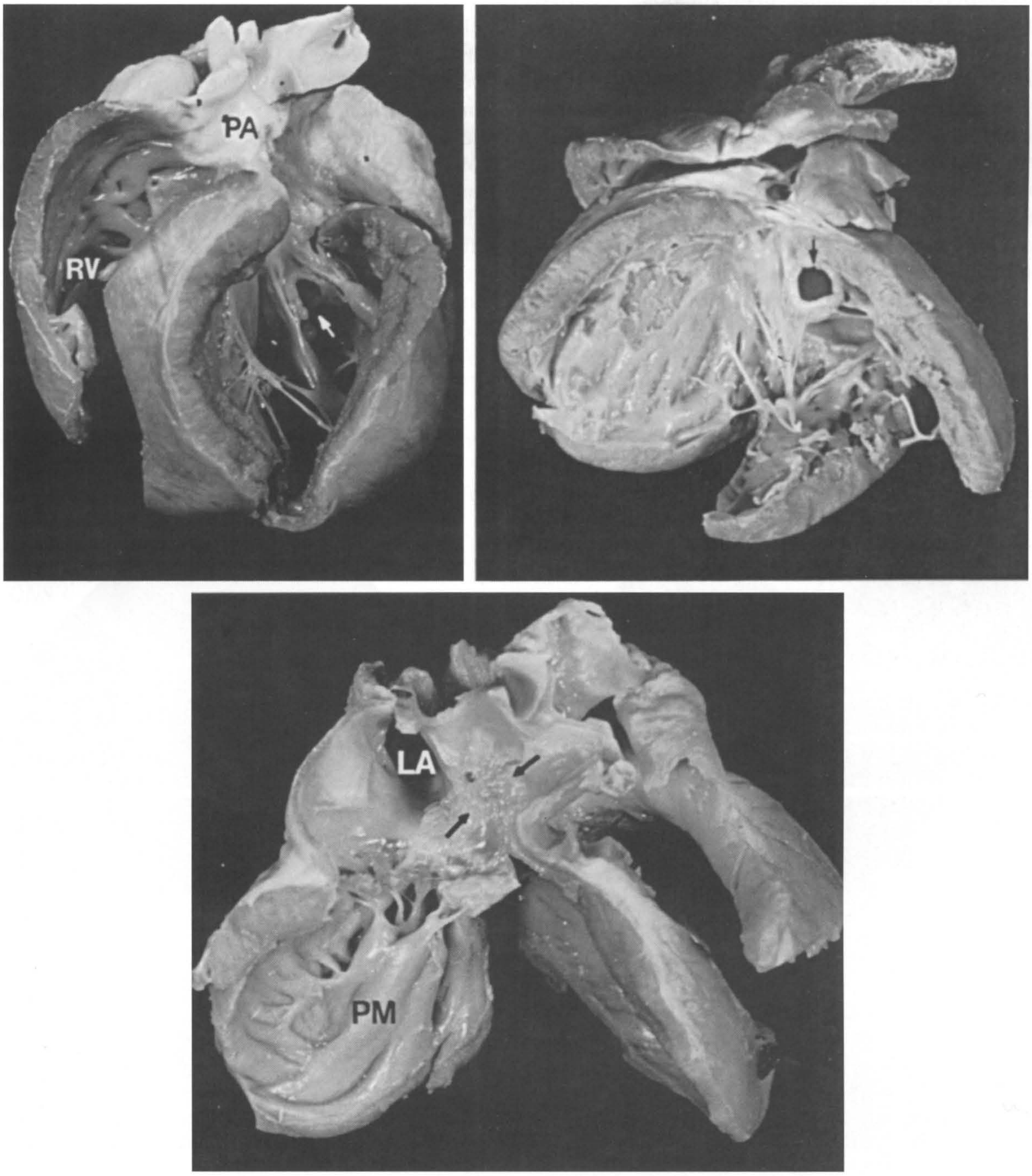


FIGURE 24–55

Mitral valve dysplasia. Three specimens are shown. *Left*, Dysplastic mitral valve from a cat. The valve cusp is thickened and the leaflet is C-shaped *(arrow)*. Both cranioventral and caudodorsal cusps were similar and resulted in an oval opening of mitral incompetency in this cat. The left auricle is markedly dilated. The right ventricle *(RV)* and pulmonary artery *(PA)* are marked. Ventricular moderator bands adjacent to the papillary muscles of the left ventricle seem prominent. *Lower panel*, Heart of a mature cat with diabetes and congestive heart failure. The open left ventricle shows a singular papillary muscle *(PM)* with relatively short chordae tendineae attaching to an abnormal mitral valve. Jet lesions *(arrows)* are evident in the opened left atrium *(LA)*. *Right panel*, A ring-type mitral valve dysplasia in a dog *(arrow)*. This dog also had a patent ductus arteriosus (not shown). (From Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 929, with permission.)

Malformations of the atrioventricular valves comprise up to 17 percent of cardiac malformations reported in cats[22] and are also common in large-breed dogs (see Table 24–1). Diagnosis can be inferred from physical examination, radiography (see Fig. 7–4), and ECG. Definitive diagnosis requires echocardiography. A malformed atrioventricular valve, as a general rule, is incompetent. In some cases, careful echocardiographic and catheterization studies may demonstrate valvular stenosis as well. In many ways, the pathophysiology and clinical course of congenital atrioventricular valve dysplasia is similar to that of acquired degenerative valvular disease in the dog (chapter 25).

PATHOPHYSIOLOGY

Principal findings in most cases of mitral or tricuspid valve dysplasia are (1) valve regurgitation with volume overloading of the ipsilateral cardiac chambers and limited cardiac output; (2) ipsilateral atrial dilation with eccentric ventricular hypertrophy; (3) predisposition to cardiac arrhythmias, particularly atrial fibrillation; (4) obstructed ventricular filling in cases when valves are also stenotic; and (5) potential for right-to-left shunting through the foramen ovale or an ASD with tricuspid dysplasia. Examples of gross findings are illustrated in Figures 24–48, 24–54, and 24–55.

Atrioventricular valve insufficiency is far more com-

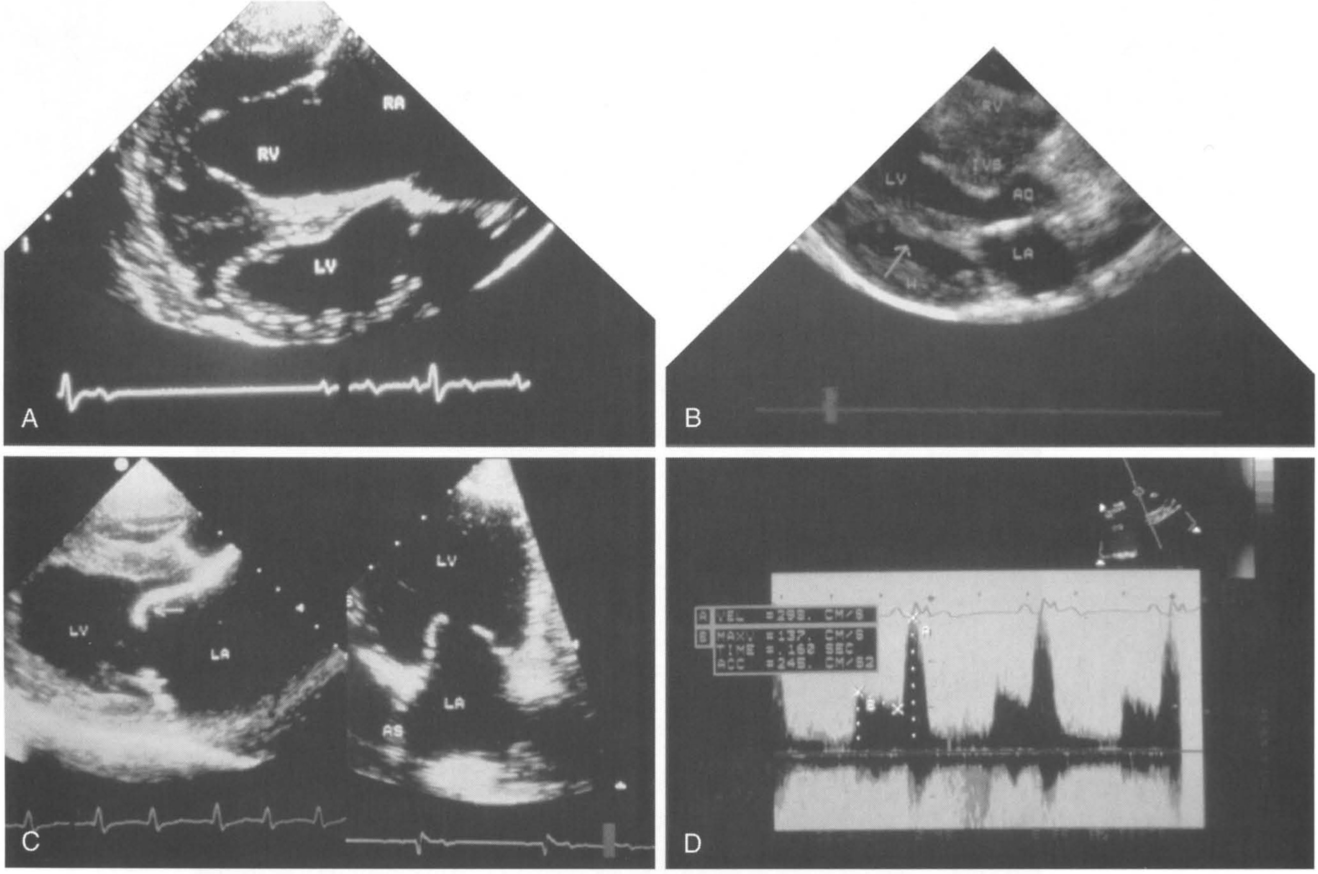


FIGURE 24–56

Echocardiograms from animals with atrioventricular valve dysplasia. (A) Long-axis, two-dimensional image from the right hemithorax of a German shepherd with tricuspid malformation. Note the dilated right atrium and ventricle *(RA, RV)* and the elongated tricuspid valve apparatus, which is connected to an abnormal, apical papillary muscle. *LV,* left ventricle. (B) Long-axis two-dimensional image from the right hemithorax of a cat with mitral valve malformation. A single, abnormal papillary muscle *(arrow)* attaches almost directly to mitral valve leaflets. The left ventricular outlet was also obstructed. *RV,* right ventricle; *IVS,* interventricular septum; *LV,* left ventricle; *Ao,* aorta; *LA,* left atrium; *W,* left ventricular posterior wall. (C) Two-dimensional echocardiograms demonstrating mitral valve stenosis in two dogs. The maximal diastolic mitral valve orifice is demonstrated in each panel. The anterior leaflets in both cases are abnormally tethered but otherwise mobile, producing a characteristic bowing toward the left ventricle *(LV)* as pressure builds behind the stenotic valve. *LA,* left atrium; *AS,* interatrial septum. (D) Continuous wave Doppler echo recording from a dog with tricuspid stenosis. The early diastolic filling pattern is prolonged *(x··x),* and the atrial contribution to ventricular filling is markedly exaggerated, with a peak velocity approximately five times normal.

mon than valve stenosis; however, both can be present in a malformed valve (Fig. 24–56). When valve dysplasia causes stenosis, a diastolic pressure gradient can be recorded by Doppler echo across the affected valve; transvalvular flow velocity will be increased and pressure decay prolonged above normal values (Fig. 24–56*D*).[54, 91] Valvular regurgitation leads to prominent *cv* waves in the atrial pressure curve, and ventricular diastolic pressures increase due to volume overload and ventricular dilatation.

MITRAL VALVE DYSPLASIA

Mitral valve dysplasia may be the most commonly recognized congenital heart lesion of cats.[2, 8, 198] The cause is unknown but a genetic basis undoubtedly exists in certain canine breeds such as the bull terrier, Great Dane, German shepherd, and a number of larger breeds (see Table 24–1); however, breeding trials have not been reported.

LESIONS

GROSS MORPHOLOGY. A spectrum of lesions has been identified (chapter 36), including shortening, rolling, notching, and thickening of the valve leaflets, fusion and thickening or elongation of the chordae tendineae, direct insertion of the valve cusp into a papillary muscle, atrophy or hypertrophy of the papillary muscles, and upward malpositioning of the papillary muscles leading to a horizontal alignment of the cords (Figs. 24–48, 24–55, 24–56).[191, 195] Valve stenosis is less common (Fig. 24–56*C*), but when present, it coexists with valve regurgitation.[91] Concurrent malformations, particularly subvalvular aortic stenosis, may be recognized in affected dogs.

CLINICAL FINDINGS

CLINICAL SIGNS. Many animals are asymptomatic, with mild lesions. Presenting signs, if any, are referable to exercise intolerance or congestive heart failure.

PHYSICAL EXAMINATION. The hallmark finding is a holosystolic murmur heard best over the left apex or along the left apical sternal border in cats. Rarely, a soft diastolic rumble is auscultated over the inflow tract of the ventricle, suggesting concurrent valvular stenosis or severe regurgitation. A loud gallop may be detected. Murmurs of other malformations may be evident.

RADIOGRAPHY. Thoracic radiographs demonstrate left-sided cardiomegaly (Fig. 24–57*A*; see also Figs. 7–4, 7–5). Left-sided congestive heart failure can occur in severe cases and may be diagnosed from physical examination and thoracic radiography.

ELECTROCARDIOGRAPHY. Atrial arrhythmias are a consequence of the left atrial dilatation that develops with this lesion (Fig. 24–58*A*).[91, 195, 199] Ventricular pre-excitation due to anomalous atrioventricular pathways also has been recognized with mitral valve malformation in both cats and dogs. An ECG may also indicate atrial and ventricular enlargement (substantiated by thoracic radiography and echocardiography).

ECHOCARDIOGRAPHY. Left atrial and left ventricular enlargement, as well as abnormal location, shape, motion, or attachment of the valve apparatus, may be

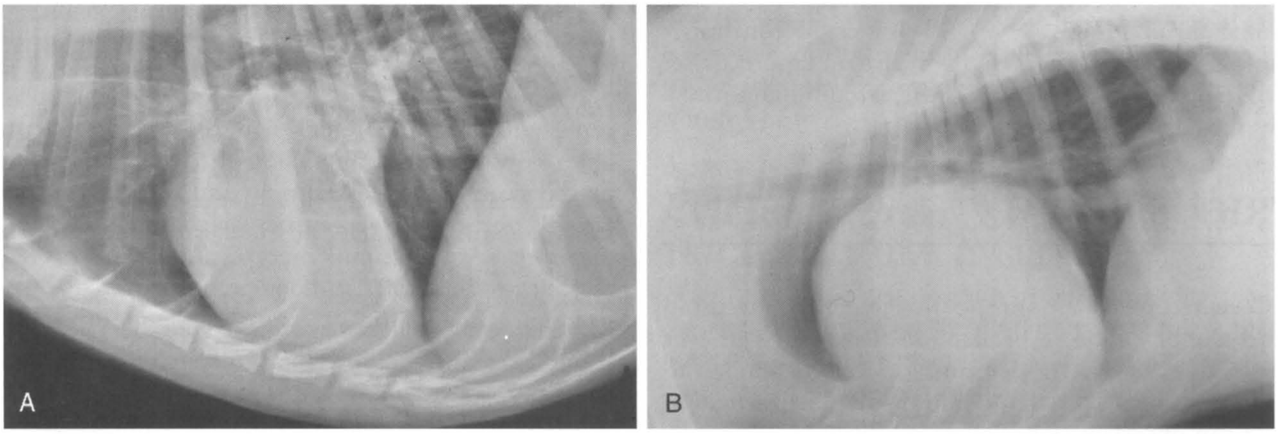


FIGURE 24–57

Radiographs from dogs with atrioventricular valve malformations. (A) Lateral radiograph from a dog with mitral valve malformation and incipient left-sided heart failure. Note the considerable left atrial dilatation and pulmonary interstitial densities. (B) Lateral radiograph from a dog with tricuspid valve dysplasia. The cranial cardiac border is quite rounded, and the heart is widened, with increased sternal contact. The caudal vena cava is displaced dorsally, supporting the assessment of right-sided enlargement.

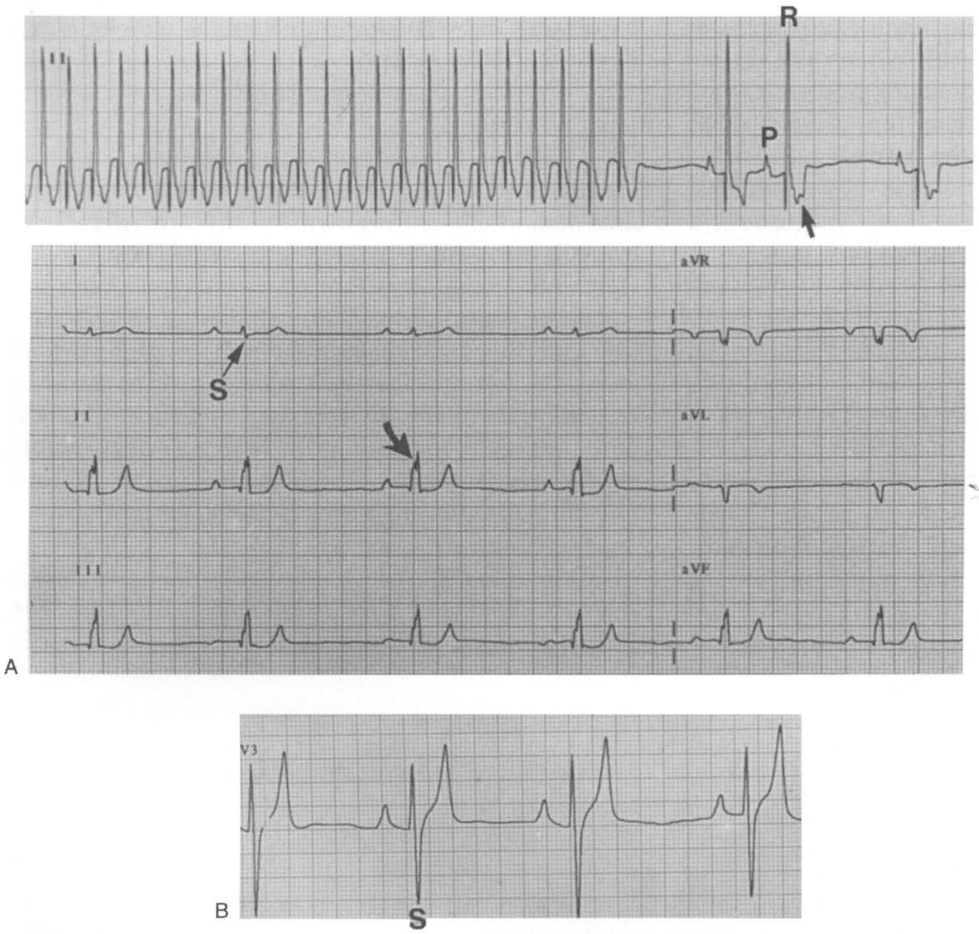


FIGURE 24–58

Electrocardiograms from two dogs with atrioventricular valve malformation. (A) ECG rhythm strip from a dog with mitral dysplasia. The initial portion of the ECG shows a nonsustained, re-entrant, supraventricular tachycardia (subsequently shown to be related to an accessory atrioventricular pathway). The last two complexes demonstrate enlarged P waves *(P)*, tall R waves *(R)*, and retrograde P waves *(arrow)* in the ST segment. Lead II at 25 mm/sec; 5 mm = 1 mV. (B) Intraventricular conduction disturbance in a dog with tricuspid dysplasia. Note the jagged R waves in leads II *(arrow)* and aVF. Small S waves *(S)* in lead I are not normal and suggest right ventricular hypertrophy. The left lower thoracic leads are often helpful in recognizing right ventricular enlargement (as shown here, lead V3 is characterized by deep S waves typical of right ventricular hypertrophy).

imaged (Fig. 24–56). Left ventricular function is variable and may deteriorate with time. Doppler echo studies can document a regurgitant jet, valvular stenosis, or both (Fig. 24–56*D*).

CARDIAC CATHETERIZATION. Angiocardiograms demonstrate a dilated ventricle, regurgitant valve orifice, and dilated atrium (Fig. 24–59). Clearance of contrast is markedly delayed when there is cardiac failure or severe regurgitation. Potential catheterization abnormalities have been discussed.

TRICUSPID VALVE DYSPLASIA

Certain breeds are prone to congenital tricuspid valve malformation, especially the Labrador retriever (see Table 24–1). A spectrum of lesions similar to those described earlier for mitral valve malformation has been observed (Figs. 24–54, 24–56*A, D*).

LESIONS

GROSS MORPHOLOGY. Affected dogs have a tendency for multiple congenital defects, including pulmonic stenosis, atrial septal defect, and ventricular pre-excitation.[196] Valve stenosis can occur (Fig. 24–56*A, D*) and may be severe in some cases (tricuspid atresia has been discussed previously). Additionally, dogs with tricuspid dysplasia can have fusion of papillary muscles, patency of the foramen ovale, and fibrinous epicarditis over the dilated right atrium. Tricuspid abnormalities also have been recognized in keeshonden with tetralogy of Fallot.[24]

Whether or not some cases of tricuspid dysplasia represent Ebstein's anomaly is unresolved.[197, 200] In the latter condition, the anomalous tricuspid valve is displaced down into the ventricle and there is an "atrialized" portion of the ventricular chamber. Definitive diagnosis requires simultaneous intracardiac pressure and electrode studies to document a ventricular electrogram but an atrial pressure curve in the ventral portion of the right atrium near the displaced valve.

CLINICAL FINDINGS

CLINICAL SIGNS. Most affected animals are clinically normal as puppies and kittens. Occasionally, severely affected kittens present with CHF.

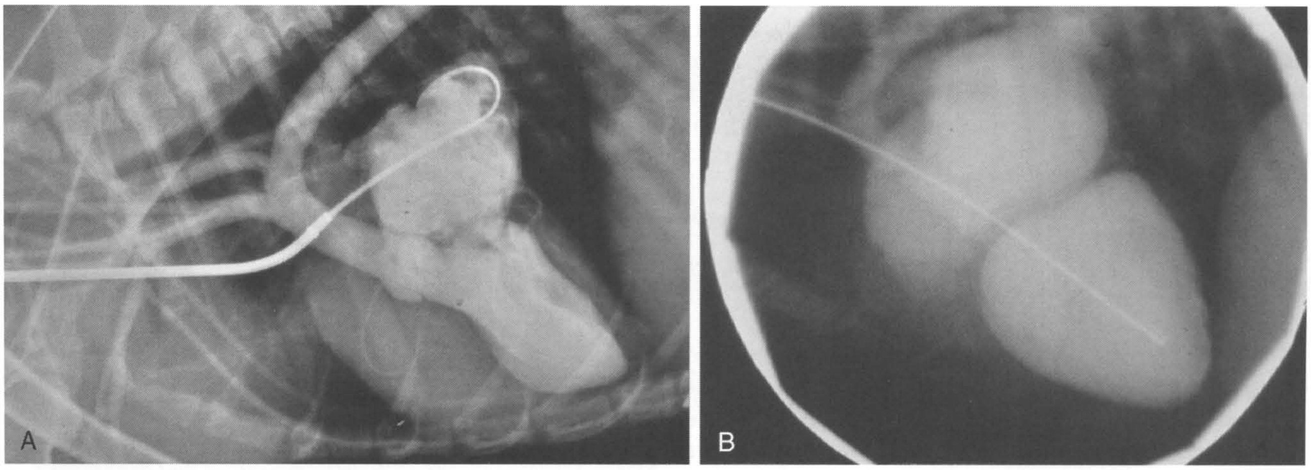


FIGURE 24–59

Angiocardiograms from two cases of congenital mitral valve malformation. (A) Transseptal catheterization of the left atrium demonstrating severe left atrial dilatation and a narrowed, funnel-shaped mitral orifice in a dog with mitral stenosis. (B) Left ventricular study in a cat demonstrates severe mitral regurgitation with dilatation of the left ventricle, left atrium, and left auricle (which projects cranially from the atrium).

PHYSICAL EXAMINATION. Typically, a holosystolic murmur is heard best over the tricuspid valve area and radiates dorsally over the right hemithorax. Rarely, a soft diastolic rumble is auscultated, suggesting concurrent valvular stenosis or severe regurgitation. The intensity of the murmur does not correlate well with lesion severity, and some dogs (especially puppies) with severe malformation have relatively soft systolic murmurs. In other dogs, a palpable precordial thrill accompanies a loud, harsh holosystolic murmur. Murmurs related to other malformations may be evident. Jugular venous pressure is normal unless right-sided CHF has developed, in which case ascites (but uncommonly pleural effusion) is present.

RADIOGRAPHY. Thoracic radiographs demonstrate right-sided cardiomegaly, particularly right atrial enlargement, often with marked apex shifting to the left (see Figs. 7–7; 24–57*B*).[194, 196, 197] The radiographic interpretation can be confusing without concurrent echocardiography.

ELECTROCARDIOGRAPHY. The ECG is generally abnormal, with intraventricular conduction disturbances and right ventricular hypertrophy evident in the left precordial leads (Fig. 24–58*B*). The P waves are typically very wide and may be increased in voltage as well. Atrial arrhythmias due to atrial dilation are common. Ventricular pre-excitation due to anomalous atrioventricular pathways also has been recognized in dogs with tricuspid dysplasia, and it seems most prevalent with concurrent atrial septal defect (as in children) in Labrador retrievers.

ECHOCARDIOGRAPHY. Definitive diagnosis requires echocardiography. Abnormal location, shape, motion, or attachment of the valve apparatus is observed by 2-D echo. A typical finding is the presence of a large, fused papillary muscle instead of the normally small, discrete muscles. The right atrium is often cavernous, and the right ventricle is also dilated unless the valve is significantly stenotic (Fig. 24–56*A*). Other congenital lesions may be identified. M-mode echo demonstrates right ventricular dilation and paradoxic ventricular septal motion. Doppler echo demonstrates a regurgitant jet, valvular stenosis, or both (see Figs. 8–18; 24–56*D*).

CARDIAC CATHETERIZATION. Catheterization is complementary but rarely necessary if a high-quality echocardiogram has been obtained. Angiography demonstrates a dilated ventricle, regurgitant valve orifice, and dilated atrium. Clearance of contrast is markedly delayed with cardiac failure or severe regurgitation. Potential pressure abnormalities have been discussed previously.

NATURAL HISTORY OF MITRAL AND TRICUSPID VALVE DYSPLASIA

Generally, the lesions are tolerated for many years; however, in other cases signs of progressive valve dysfunction, cardiomegaly, atrial arrhythmias and heart failure and death ensue.[91, 191, 192, 194–198] Only the most severely affected animals are usually described in clinical reports, and these papers emphasized that heart failure and atrial arrhythmias can develop within the first year of life. We have observed the onset of heart failure from atrioventricular valve dysplasia in dogs less than 6 months of age and as old as 8 years of age. Cats

with mitral dysplasia may develop CHF early in life, live normally for many years before developing heart failure, or they may never develop clinical signs at all. Significant cardiomegaly suggests a guarded-to-poor prognosis.

CLINICAL MANAGEMENT OF MITRAL AND TRICUSPID VALVE DYSPLASIA

Treatment is supportive and similar to that described for chronic valvular disease (chapter 25). Surgical valve replacement has been done only under experimental conditions.[197] It is conceivable that a stenotic valve could be surgically opened or dilated with a balloon valvuloplasty catheter. Treatment of congestive heart failure and management of atrial fibrillation are often required in advanced cases (see Table 24–3).

MISCELLANEOUS CARDIAC DEFECTS

Many rare anatomic lesions of the heart are beyond the scope of this chapter. The following section summarizes clinically relevant aspects of cardiac and pericardial defects not yet discussed.

PERITONEOPERICARDIAL DIAPHRAGMATIC HERNIA

This is a relatively common developmental anomaly of dogs and cats.[129, 201–208, 208a] While not a true cardiac anomaly, it can be confused with other congenital and acquired conditions. It probably represents abnormal development of the septum transversum or pleuroperitoneal folds in the fetus.[204] Typically, abdominal viscera are found within the pericardial sac. Defects range from mild cases, with only omentum and a lobe of liver within the hernia sac, to the presence of multiple organs and intestinal loops adjacent to the heart. Intrapericardiac cysts have also been observed in dogs, either in isolation or in conjunction with a hernia.[209]

CLINICAL FINDINGS

CLINICAL SIGNS. The clinical signs are variable, including respiratory distress, wheezing, colic, and vomiting. Cats frequently reach maturity without apparent symptoms. A high incidence has been reported in male Persian cats.[208a]

PHYSICAL EXAMINATION. The physical examination indicates that the cardiac apex is in an abnormal position, or there is inability to auscultate the heart sounds in the usual location. A soft systolic murmur may be evident, but the genesis of this is unknown. Louder murmurs are detectable in pets with concurrent congenital heart defects. Borborygmus may be evident over the heart when there is bowel in the pericardial space. A palpable defect at the caudoventral midline or a malformation of the xiphoid or ventral abdominal wall is present in some cases.

RADIOGRAPHY. Thoracic radiographs demonstrate cardiac silhouette enlargement and altered contour, lack of normal separation between the pericardial shadow and the diaphragm, and inhomogeneity of the apparent cardiac density. Gas may be found within the pericardium, but in cats, gas-filled intestinal loops are uncommon and the clinician may misdiagnose the enlarged outline as cardiomegaly from another cause. The dorsal extent of the hernia is represented by a soft tissue density, a persistent mesothelial remnant ventral to the caudal vena cava on the lateral view. Anomalous development of the sternum may occur. Barium shows the position of the stomach and intestines, whereas a nonselective angiocardiogram may demonstrate cardiac displacement and other structures and/or fluid within the pericardial sac.

ECHOCARDIOGRAPHY. Echocardiographic examination is very useful for substantiating the diagnosis, particularly when hepatic lobes are identified within the hernia sac.

THERAPY

Surgical reduction of the hernia and replacement of abdominal contents in the peritoneal space may be indicated.[201, 205, 208] Such surgery may decrease clinical signs and prevent herniation of an abdominal organ. One must ensure that current clinical signs are related to the hernia and not a concurrent disease. We prefer not to operate on older affected cats since they seem to tolerate the condition well.

COR TRIATRIATUM

Malformations of atrial septation other than an ASD have been recognized in small animals. Cor triatriatum has been reported in a cat[210]; cor triatriatum dexter and saccular anomalies of the caudal right atrium have been described in dogs and cats.[211–218] Cor triatriatum is characterized by an additional, accessory atrial chamber, which is separated from the true atrium by a membrane, and collects the venous drainage (Fig. 24–60). When the membrane is obstructive, dilation of the venous chamber and the entering veins is evident, and congestion develops in the lungs or, in the case of

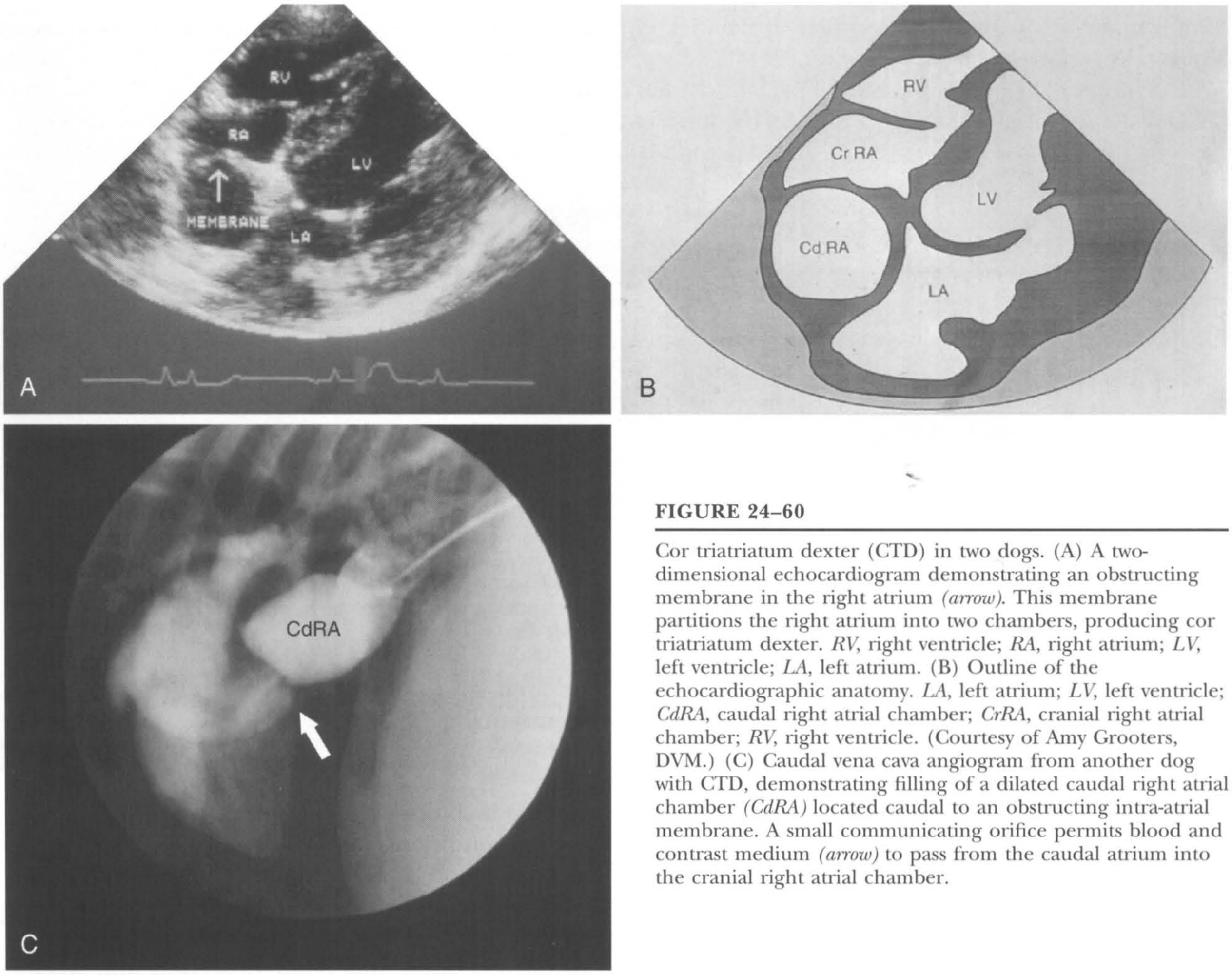


FIGURE 24–60

Cor triatriatum dexter (CTD) in two dogs. (A) A two-dimensional echocardiogram demonstrating an obstructing membrane in the right atrium *(arrow)*. This membrane partitions the right atrium into two chambers, producing cor triatriatum dexter. *RV*, right ventricle; *RA*, right atrium; *LV*, left ventricle; *LA*, left atrium. (B) Outline of the echocardiographic anatomy. *LA*, left atrium; *LV*, left ventricle; *CdRA*, caudal right atrial chamber; *CrRA*, cranial right atrial chamber; *RV*, right ventricle. (Courtesy of Amy Grooters, DVM.) (C) Caudal vena cava angiogram from another dog with CTD, demonstrating filling of a dilated caudal right atrial chamber *(CdRA)* located caudal to an obstructing intra-atrial membrane. A small communicating orifice permits blood and contrast medium *(arrow)* to pass from the caudal atrium into the cranial right atrial chamber.

a right atrial membrane, in the liver. Animals with cor triatriatum are examined for signs attributable to pulmonary edema or ascites. We have also examined cats with saccular dilations of the caudal right atrium that protruded into the left hemithorax but did not cause clinical signs. Treatment generally requires surgical resection or bypass of the obstruction.[213, 218]

ENDOCARDIAL FIBROELASTOSIS

Endocardial fibroelastosis has been reported in dogs and cats and is probably familial in some lines of Burmese and Siamese cats (see also chapter 28).[8, 219–221]

LESIONS

GROSS MORPHOLOGY. Findings include left ventricular and left atrial dilatation with severe endocardial thickening, characterized grossly by diffuse, white, opaque thickening of the luminal lining. Dogs with endocardial fibroelastosis often have thickening of the mitral valve leaflets and mitral regurgitation.

HISTOLOGIC FEATURES. In the cat, these include diffuse hypocellular, fibroelastic thickening of the endocardium, with layering of thin, randomly organized collagen and elastic fibers. Edema of the endocardium with dilation of lymphatics is prominent, and there is no evidence of myocardial inflammation or necrosis.

CLINICAL FEATURES

Early development of left or biventricular failure, generally before 6 months of age, is common. Affected animals fail to thrive. A murmur of mitral regurgitation may be auscultated. Left ventricular and atrial dilation are evident on radiographs and on the ECG. Limited echocardiographic studies suggest reduction of left ventricular myocardial function. Left ventricular diastolic pressures are elevated, compatible with ventricular stiffness, ventricular failure, or volume overload from mitral regurgitation.[221]

The diagnosis of primary endocardial fibroelastosis is, at times, tenuous, inasmuch as chronic left ventricular dilatation may lead to similar changes, particularly in the setting of mitral dysplasia, aortic stenosis, dilated

cardiomyopathy, or myocarditis. Similar difficulties in diagnosis exist in children with this disorder.[14]

Medical treatment of congestive heart failure may be effective in prolonging life. However, recovery is unlikely in actual cases of endocardial fibroelastosis.

VASCULAR ANOMALIES

These may be classified based on their location within the vascular system. Patent ductus arteriosus represents the most important vascular malformation; aortic coarctation, hypoplasia, and interruption have been rarely reported. Unilateral atresia of a pulmonary artery has been described in a cat with respiratory difficulty.[222] Coronary arteries can develop anomalously but rarely cause documented clinical disease except as previously described under pulmonic stenosis. Other major vascular defects centering on the aorta and systemic venous drainage are addressed next.

VASCULAR RING ANOMALIES

Vascular ring anomalies are characterized by malformation of the aortic fetal arch systems, with entrapment of the esophagus between the abnormal vessel(s) and the heart base. These vascular defects, especially *persistence of the right fourth aortic arch*, have been reported frequently in dogs and cats.[141, 143, 223–235] Other vascular ring anomalies include those formed by *retroesophageal subclavian arteries, double-aortic arch*, or *left aortic arch with right-sided ligamentum arteriosum.* Persistent right fourth aortic arch surrounds the esophagus with the following structures: pulmonary artery to the left; ligamentum arteriosum to the left and dorsally; right aortic arch to the right; heart base and trachea ventrally (Fig. 24–61). The cardinal feature of these defects is regurgitation of solid food because of obstruction of the esophagus, rather than circulatory dysfunction. The condition is common in German shepherd dogs and is recognized in many other canine breeds, including Irish setters and Great Danes (see Table 24–1). In the cat, the condition is uncommon. Occasionally, other cardiac defects are present, including PDA.

Diagnosis is made from the history of regurgitation at the time of weaning, evaluation of thoracic radiographs, and a barium swallow. Care must be taken not to induce aspiration pneumonia, which many of these animals develop due to recurrent regurgitation and aspiration. Depression or fever should be taken as signs to initiate broad spectrum antibiotic therapy promptly or to perform tracheal wash and then initiate treatment. The characteristic indentations of the obstructing components of a persistent right fourth aortic arch may be observed by esophageal endoscopy. Occasionally, the diagnosis is less straightforward, as with left arch and right-sided ligamentum arteriosum,[229–231, 234] and requires angiography. Differential diagnosis includes esophageal stenosis or hypoplasia.

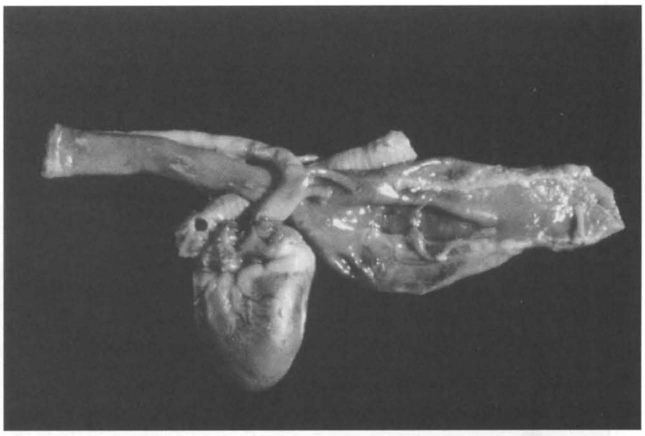


FIGURE 24–61

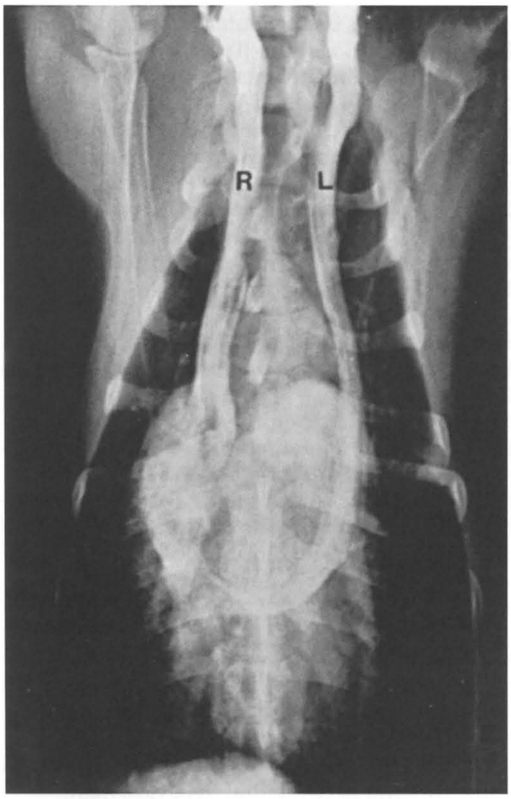
Persistent right fourth aortic arch in a cat. The specimen is viewed from the right lateral perspective. The aorta arches to the right, entrapping the esophagus between the trachea, base of the heart, and the ligamentum arteriosum (not shown). The dilated proximal esophagus is evident at the right side of the figure.

The condition is essentially that of esophageal obstruction, and significant clinical improvement can be obtained in many animals following surgery. Surgery should not be delayed and usually involves division of the ligamentum and blunt dissection and freeing of the esophagus. Residual esophageal dilation or motor dysfunction may be observed following surgery in some patients.[235, 235a]

AORTICOPULMONARY SEPTAL DEFECT

Persistent aorticopulmonary septal defect, as opposed to the PDA, is caused by failure of the truncus arteriosus to differentiate.[162–164, 236] Subsequently, shunting develops between the ascending aorta and pulmonary artery. Although a clinical condition similar to that of PDA can develop, in most cases pulmonary hypertension occurs during the first year of life, and clinical signs are similar to those in dogs that develop Eisenmenger's syndrome owing to other defects.

Management is similar to that for a reversed PDA. Surgery should not be attempted if pulmonary vascular resistance is markedly elevated; it is difficult in left-to-right shunting defects unless cardiopulmonary bypass is available. This defect is not synonymous with a short, wide PDA that sometimes is referred to as a "window."



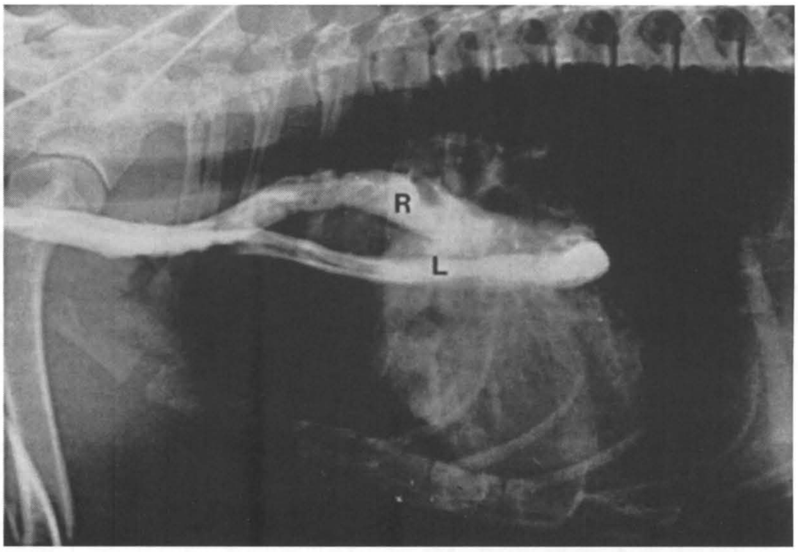


FIGURE 24–62

Persistent left cranial vena cava in a dog. Contrast was injected simultaneously into both the right and left jugular veins. The normal right cranial vena cava is evident *(R)* as well as a persistent left vena cava *(L)*. Notice that the left vena cava empties in the caudal portion of the right atrium into the coronary sinus. (From Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 942, with permission.)

VENOUS ANOMALIES

Thoracic venous anomalies rarely cause cardiac problems in small animals. Total or partial anomalous pulmonary venous return has been reported in a dog and behaves functionally as a left-to-right shunt at the atrial level.[119] Abnormalities of abdominal venous drainage, such as *patent ductus venosus,* can induce hepatic encephalopathy. A relatively common venous abnormality of clinical significance during thoracic surgery is the *persistent left cranial vena cava.*[42] This vessel, normally present in the fetus as part of the left cardinal venous system, may persist and drain into the embryologically related coronary sinus in the caudal aspect of the right atrium (Fig. 24–62). Persistent left cranial vena cava may interfere with surgical exposure, particularly during surgical treatment of persistent right fourth aortic arch, but otherwise it is of no known functional significance. As with right fourth aortic arch, this vascular anomaly is common in German shepherds and has been reported in other canine breeds, as well as in cats.[42, 175, 237] Division of this vessel generally poses no clinical problem provided the normal right cranial vena cava is also present. Absence of the caudal vena cava,[238] venous aneurysms,[239] and aberrant caudal venous return via a left azygos[240] have been reported but are rare.

REFERENCES

1. Patterson DF. Congenital heart disease in the dog. Ann NY Acad Sci 127:541, 1965
2. Bolton GR, Liu SK. Congenital heart diseases of the cat. Vet Clin North Am (Sm Anim Pract) 7:341, 1977
3. Severin GA. Congenital and acquired heart disease. J Am Vet Med Assoc 151:1733, 1967
4. Bonagura JD. Congenital heart disease. *In* Ettinger SJ (ed). Textbook of Veterinary Internal Medicine: Diseases of the Dog and the Cat. 3rd ed. Philadelphia, WB Saunders, 1989, p 976
5. Detweiler DK, Patterson DF. The prevalence and types of cardiovascular disease in dogs. Ann NY Acad Sci 127:481, 1965
6. Ettinger SJ, Suter PF. Congenital heart disease. *In* Ettinger SJ (ed). Textbook of Veterinary Internal Medicine. Philadelphia, WB Saunders, 1975
7. Ettinger SJ, Suter PF. Canine Cardiology. Philadelphia, WB Saunders, 1970
8. Liu SK. Pathology of feline heart disease. Vet Clin North Am (Sm Anim Pract) 7:323, 1977
9. Patterson DF. Hereditary congenital heart defects in dogs. J Small Anim Pract 30:153, 1989
10. Patterson DF. Canine congenital heart disease: Epidemiology and etiological hypotheses. J Small Anim Pract 12:263, 1971
11. Patterson DF. Epidemiologic and genetic studies of congenital heart disease in the dog. Circ Res 23:171, 1968
12. Patterson DF, Medway W. Hereditary diseases of the dog. J Am Vet Med Assoc 149:1741, 1966
13. Van Mierop LSH. Pathology and pathogenesis of the

common cardiac malformations. Cardiol Clin 2:28, 1970
14. Friedman WF. Congenital heart disease in infancy and childhood. *In* Braunwald E (ed). Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB Saunders, 1992, p 887
14a. Tidholm A. Retrospective study of congenital heart defects in 151 dogs. J Small Anim Pract 38:94, 1997
15. Detweiler DK. Genetic aspects of cardiovascular diseases in animals. Circulation 30:114, 1964
16. Shive RJ, Hare WCD, Patterson DF. Chromosome studies in dogs with congenital cardiac defects. Cytogenetics 4:340, 1965
17. Patterson DF, Hare WCD, Shive RJ, Luginbuhl H. Congenital malformations of the cardiovascular system associated with chromosomal abnormalities. Zentralbl Vet Med 13:669, 1966
18. Pyle RL, Patterson DF, Chacko S. The genetics and pathology of discrete subaortic stenosis in the Newfoundland dog. Am Heart J 92:324, 1976
19. Stur I, Roth A, Muller S. Investigation into a familial accumulated occurrence of congenital cardiac anomalies in Siamese and Oriental short-haired cats. Kleintierpraxis 36:85, 1991
20. Ruble RP, Hird DW. Congenital abnormalities in immature dogs from a pet store: 253 cases (1987–1988). J Am Vet Med Assoc 202:633, 1993
21. Bright JM, Holmberg DL. The cardiovascular system. *In* Hoskins J (ed). Veterinary Pediatrics: Dogs and Cats from Birth to Six Months of Age. Philadelphia, WB Saunders, 1990, p 43
22. Harpster N, Zook B. The cardiovascular system. *In* Holzworth J (ed). Diseases of the Cat: Medicine and Surgery. Philadelphia, WB Saunders, 1987, p 820
23. Patterson DF, Pyle RL, Buchanan JW, et al. Hereditary patent ductus arteriosus and its sequelae in the dog. Circ Res 29:1, 1971
24. Patterson DF, Pyle RL, Van Mierop L, Melbin J, Elson M. Hereditary defects of the conotruncal septum in Keeshond dogs: Pathologic and genetic studies. Am J Cardiol 34:187, 1974
25. Patterson DF, Pexieder T, Schnarr WR, et al. A single major-gene defect underlying cardiac conotruncal malformations interferes with myocardial growth during embryonic development: Studies in the CTD line of keeshond dogs. Am J Hum Genet 52:388, 1993
26. Van Mierop LS, Patterson DF, Schnarr WR Hereditary conotruncal septal defects in Keeshond dogs: Embryologic studies. Am J Cardiol 40:936, 1977
27. Perkins RL. Multiple congenital cardiovascular anomalies in a kitten. J Am Vet Med Assoc 160:1430, 1972
28. Pyle RL, Patterson DF. Multiple cardiovascular malformations in a family of boxer dogs. J Am Vet Med Assoc 160:965, 1972
29. Ogburn PN, Peterson M, Jeraj K, et al. Multiple cardiac anomalies in a family of Saluki dogs. J Am Vet Med Assoc 179:57, 1981
30. Ware WA, Bonagura JD. Multiple congenital cardiac anomalies and Eisenmenger's syndrome in a dog. Compend Cont Educ Pract Vet 10:932, 1988
31. Philips R, Hoover JP, Henry GA. Multiple congenital defects in a Blue Merle Sheltie. Canine Pract 15:4, 1990
32. Rochat MC, Lattimer JC, Miller MA, et al. Multiple cardiac anomalies in a cat. J Am Vet Med Assoc 201:1049, 1992
33. Hunt GB, Church DB, Malik R, et al. A retrospective analysis of congenital cardiac anomalies (1977–1989). Aust Vet Pract 20:70, 1990
34. Buchanan JW. Causes and prevalence of cardiovascular disease. *In* Kirk RW, Bonagura JD (eds). Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 647
34a. Monnet E, Orton EC, Gaynor J, et al. Diagnosis and surgical repair of partial atrioventricular septal defects in two dogs. J Am Vet Med Assoc 211:569, 1997
35. Trautvetter E. Evolution of the electrocardiogram in young dogs with congenital heart disease leading to right ventricular hypertrophy. J Electrocardiol 14:275, 1981
35a. Nakayama T, Wakao Y, Ishikawa R, Takahashi M. Progression of subaortic stenosis detected by continuous wave Doppler echocardiography in a dog. J Vet Intern Med 10:97, 1996
36. Suter PF, Lord PF. Cardiac diseases. *In* Suter PF (ed). Thoracic Radiography of the Dog and Cat. Wettswil, Switzerland, Peter F. Suter, 1984, p 351
37. Stickle RL, Anderson LK. Diagnosis of common congenital heart anomalies in the dog using survey and nonselective contrast radiography. Vet Radiol 28:6, 1987
38. Goodwin JK, Lombard CW. The electrocardiographic and radiographic features of common congenital heart defects. Vet Med 85:48, 1990
39. Buchanan JW, Patterson DF. Selective angiocardiography in dogs with congenital cardiovascular disease. J Am Vet Radiol Soc 6:21, 1965
40. Bonagura JD, Myer CW, Pensinger RR. Angiocardiography. Vet Clin North Am (Small Anim Pract) 12:239, 1982
41. Lord PF, Wood A, Liu SK, Tilley LP. Left ventricular angiocardiography in congenital mitral valve insufficiency of the dog. J Am Vet Med Assoc 166:1069, 1975
42. Buchanan JW. Persistent left cranial vena cava in dogs: angiocardiography, significance, and coexisting anomalies. J Am Vet Radiol Soc 4:1, 1963
43. Sisson DD, Luethy M, Thomas WP. Ventricular septal defect accompanied by aortic regurgitation in five dogs. J Am Anim Hosp Assoc 27:441, 1991
44. Goodwin JK, Lombard C. Angio- and echocardiography: Viewing heart defects in more detail. Vet Med 85:64, 1990
45. Buchanan JW. Pulmonic stenosis caused by single coronary artery in dogs: Four cases (1965–1984). J Am Vet Med Assoc 196:115, 1990
46. Bonagura JD, Herring DS. Echocardiography II: Congenital heart disease. Vet Clin North Am (Small Anim Pract) 15:1195, 1985
47. Darke PGG. Congenital heart disease in dogs and cats. J Small Anim Pract 30:599, 1989
48. Gaber CE. Doppler echocardiography. Probl Vet Med 3:479, 1991
49. Kaplan PM. Congenital heart disease. Probl Vet Med 3:500, 1991
50. Matic SE. Congenital heart disease in the dog. J Small Anim Pract 29:743, 1988
51. Moise NS. Doppler echocardiographic evaluation of congenital cardiac disease. J Vet Intern Med 3:195, 1989
52. Wingfield WE, Boon JA. Echocardiography for the diagnosis of congenital heart defects in the dog. Vet Clin North Am (Small Anim Pract) 17:735, 1987
53. Lehmkuhl LB, Bonagura JD. Comparison of Doppler transducer placement sites for estimating the severity of subaortic stenosis in dogs. Am J Vet Res 55:192, 1994
54. Goldberg SJ, Allen HD, Marx GR, et al. Doppler Echocardiography. 2nd ed. Philadelphia, Lea & Febiger, 1988
55. Weyman AE. Principles and Practice of Echocardiography. Philadelphia, Lea & Febiger, 1994

56. Fingland RB, Bonagura JD, Myer CW. Pulmonic stenosis in the dog: 29 cases (1975–1984). J Am Vet Med Assoc 189:218, 1986
57. Buchanan JW, Pyle RL. Cardiac tamponade during catheterization of a dog with congenital heart disease. J Am Vet Med Assoc 149:1056, 1966
58. Martin MWS, Godman M, Fuentes VL, et al. Assessment of balloon pulmonary valvuloplasty in six dogs. J Small Anim Pract 33:443, 1992
59. Lombard CW, Ackerman N, Berry CR, et al. Pulmonic stenosis and right-to-left atrial shunt in three dogs. J Am Vet Med Assoc 194:71, 1989
60. Ringwald RJ, Bonagura JD. Tetralogy of Fallot in the dog: Clinical findings in 13 cases. J Am Anim Hosp Assoc 24:33, 1988
60a. Baim DS, Grossman W. Cardiac catheterization, angiography, and intervention. 5th Ed. Baltimore, Williams & Wilkins, 1996
61. Legendre AM, Appleford MD, Eyster GE, Dade AW. Secondary polycythemia and seizures due to right-to-left shunting patent ductus arteriosus in a dog. J Am Vet Med Assoc 164:1198, 1974
62. Custer MA, Kantor AF, Gilman RA, DeRiemer RH. Correction of pulmonic stenosis. J Am Vet Med Assoc 139:565, 1961
63. Hamlin RL, Marsland WP, Rudy RL, Drenan DM. Atypical clinical findings in a dog with pulmonic stenosis. J Am Vet Med Assoc 142:520, 1963
64. Weirich WE, Bisgard GE, Will JA, Rowe GG. Myocardial infarction and pulmonic stenosis in a dog. J Am Vet Med Assoc 159:315, 1971
65. Lowensohn HS, Khouri EM, Gregg DE, et al. Phasic right coronary artery blood flow in conscious dogs with normal and elevated right ventricular pressure. Circ Res 39:760, 1976
66. Hawe RS. Pulmonic stenosis in a cat. J Am Anim Hosp Assoc 17:777, 1981
67. Jacobs G, Mahaffey M, Rawlings CA. Valvular pulmonic stenosis in four Boykin spaniels. J Am Animal Hosp Assoc 26:247, 1990
68. Patterson DF, Haskins ME, Schnarr WR. Hereditary dysplasia of the pulmonary valve in beagle dog. Am J Cardiol 47:631, 1981
69. Willard MD, Eyster GE. Double-chambered right ventricle in two dogs. J Am Vet Med Assoc 178:486, 1981
70. Polzin DJ, Ogburn P. Isolated pulmonary valvular insufficiency in a dog. J Am Anim Hosp Assoc 17:301, 1981
71. Eyster GE, Keller WF. Congenital pulmonic valve insufficiency in a dog. J Am Vet Med Assoc 164:599, 1974
72. Breznock EM. Surgical relief of pulmonic stenosis. *In* Bojrab, M (ed). Current Techniques in Small Animal Surgery. Philadelphia, WB Saunders, 1990, p 513
73. Breznock EM, Wood GL. A patch-graft technique for correction of pulmonic stenosis in dogs. J Am Vet Med Assoc 169:1090, 1976
74. Ford RB, Spaulding GL, Eyster GE. Use of an extracardiac conduit in the repair of supravalvular pulmonic stenosis in a dog. J Am Vet Med Assoc 172:922, 1978
75. Orton EC, Bruecker KA, McCracken TO. An open patch-graft technique for correction of pulmonic stenosis in the dog. Vet Surg 19:148, 1990
76. Shores A, Weirich W. A modified pericardial patch graft technique for correction of pulmonic stenosis in the dog. J Am Anim Hosp Assoc 21:812, 1985
77. Washizu M, Kawamura M, Kobayashi K, et al. Improved heavy exercise tolerance after correction of mild pulmonic stenosis. Jap J Vet Sci 51:441, 1989
78. Whiting PG, Breznock GL, Pendray DL, Strack DR. Double outlet right ventricle for relief of pulmonic stenosis in dogs. An experimental study. Vet Surg 13:64, 1984
79. Bright JM, White RI Jr, Mitchell SE, Gardner TJ. Percutaneous balloon valvuloplasty for treatment of pulmonic stenosis in a dog. J Am Vet Med Assoc 191:995, 1987
80. Sisson DD, MacCoy DM. Treatment of congenital pulmonic stenosis in two dogs by balloon valvuloplasty. J Vet Intern Med 2:92, 1988
81. Brownlie SE, Cobb MA, Chambers J, et al. Percutaneous balloon valvuloplasty in four dogs with pulmonic stenosis. J Small Anim Pract 32:165, 1991
82. Flickinger GL, Patterson DF. Coronary lesions associated with congenital subaortic stenosis in the dog. J Pathol Bacteriol 93:133, 1967
83. Kvart C. Congenital heart defects in the dog. Svensk Veterinartidning 38:15, 1986
84. O'Grady MR, Holmberg DL, Miller CW, et al. Canine congenital aortic stenosis: A review of the literature and commentary. Can Vet J 30:811, 1989
85. Patterson DF, Flickinger GL. Subaortic stenosis in a boxer. Clinico-Pathologic Conference. J Am Vet Med Assoc 145:363, 1964
86. Patterson DF, Detweiler DK. Predominance of German shepherd and boxer breeds among dogs with congenital subaortic stenosis. Am Heart J 65:429, 1963
87. Pyle RL, Lowensohn HS, Khouri EM, et al. Left circumflex coronary artery hemodynamics in conscious dogs with congenital subaortic stenosis. Circ Res 33:34, 1973
88. Sisson D. Fixed and dynamic subvalvular aortic stenosis in dogs. *In* Kirk RW, Bonagura JD (eds). Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 760
89. Liu S. Supravalvular aortic stenosis with deformity of the aortic valve in a cat. J Am Vet Med Assoc 152:55, 1968
90. Stepien RL, Bonagura JD. Aortic stenosis; Clinical findings in six cats. J Small Anim Pract 32:341, 1991
91. Lehmkuhl LB, Ware WA, Bonagura JD. Mitral stenosis in 15 dogs. J Vet Intern Med 8:2, 1994
92. Buoscio DA, Sisson D, Zachary JF, et al. Clinical and pathological characterization of an unusual form of subvalvular aortic stenosis in four golden retriever puppies. J Am Anim Hosp Assoc 30:100, 1994
93. Goodwin JK, Lombard CW. Identifying congenital heart defects using clues from the physical exam. Vet Med 85:40, 46, 1990
94a. Valdes-Cruz LM, Jones M, Scagnelli S, et al. Prediction of gradients in fibrous subaortic stenosis by continuous wave two-dimensional Doppler echocardiography: Animal studies. J Am Coll Cardiol 5:1363, 1985
94b. Lehmkuhl LB, Bonagura JD, Jones DA, Stepien RL. Comparison of catheterization and Doppler-derived gradients in a canine model of subaortic stenosis. J Am Soc Echocardiogr 8:611, 1995
95. Wingfield WE, Boon JA, Miller CW. Echocardiographic assessment of congenital aortic stenosis in dogs. J Am Vet Med Assoc 183:673, 1983
96. O'Grady MR. The incidence of aortic valve insufficiency in congenital canine aortic stenosis: A Doppler echocardiographic study; Abstract. J Vet Intern Med 4:129, 1990
97. Aronson E, McCaw D. Congenital cardiac disease in dogs [aortic stenosis]. Mod Vet Pract 65:687, 1984
98. Muna WFT, Ferrans VJ, Pierce JE, Roberts WC. Discrete subaortic stenosis in Newfoundland dogs: Association of infective endocarditis. Am J Cardiol 41:746, 1978
99. Eyster GE, Anderson LK, Cords GB. Aortic regurgitation in the dog. J Am Vet Med Assoc 168:138, 1976

100. Breznock EM, Whiting P, Pendray D, et al. Valved apicoaortic conduit for relief of left ventricular hypertension caused by discrete subaortic stenosis in dogs. J Am Vet Med Assoc 182:51, 1983
101. Linn KA, Orton EC. Closed transventricular dilation of discrete subvalvular aortic stenosis in dogs. Vet Surg 20:340, 1991
102. Muir GD, Panciera DL, Fowler JD, et al. Medical and surgical management of aortic stenosis in a dog. Can Vet J 30:894, 1989
103. Komtebedde J, Ilkiw J. Resection of subvalvular aortic stenosis. Vet Surg 22:419, 1993
103a. Monnet E, Orton EC, Gaynor JS, et al. Open resection for subvalvular aortic stenosis in dogs. J Am Vet Med Assoc 209:1255, 1996
103b. Dhokarikar P, Caywood DD, Ogburn PN, et al. Closed aortic valvotomy: A retrospective study in 15 dogs. J Am Anim Hosp Assoc 31:402, 1995
104. DeLellis LA, Thomas WP, Pion PD. Balloon dilation of congenital subaortic stenosis in the dog. J Vet Intern Med 7:153, 1993
105. Herrtage ME, Gorman NT, Jefferies AR. Coarctation of the aorta in a dog. Vet Radiol Ultrasound 33:25, 1992
106. Eyster GE, Carrig CB, Baker B, et al. Coarctation of the aorta in a dog. J Am Vet Med Assoc 169:426, 1976
107. Sandusky GE, Breitschwerdt ER. Tubular hypoplasia of the ascending aorta and patent ductus arteriosus in a dog. J Am Vet Med Assoc 176:536, 1980
108. Nichols JB, Eyster GE, Dulisch ML, et al. Aortic interruption in a dog. J Am Vet Med Assoc 174:1091, 1979
109. Hamlin RL, Smith CR, Smetzer DL. Ostium secundum type interatrial septal defects in the dog. J Am Vet Med Assoc 143:149, 1963
110. Eyster GE, Anderson LK, Krehbeil JD, et al. Surgical repair of atrial septal defect in dog. J Am Vet Med Assoc 169:1081, 1976
111. Troy GC, Turnwald GH. Atrial fibrillation and abnormal ventricular conduction presented as right bundle branch block in a dog with an atrial septum primum defect. J Am Anim Hosp Assoc 15:417, 1979
112. Jeraj K, Ogburn PN, Johnston GR, et al. Atrial septal defect (sinus venosus type) in a dog. J Am Vet Med Assoc 177:342, 1980
113. Farrow CS. Atrial septal defect in a kitten. Mod Vet Pract 65:281, 1984
114. Church DB, Allan GS. Atrial septal defect and Eisenmenger's syndrome in a mature cat. Aust Vet J 67:380, 1990
115. Goodwin JK, Cooper RC Jr. Understanding the pathophysiology of congenital heart defects. Vet Med 87:650, 1992
116. Kirkberger RM, Berry WL. Atrial septal defect in a dog: The value of Doppler echocardiography. J S Afr Vet Assoc 63:43, 1992
117. Liu SK, Ettinger SJ. Persistent common atrioventricular canal in two cats. J Am Vet Med Assoc 153:556, 1968
118. Hagler DJ, Edwards WD, Seward JB, et al. Standardized nomenclature of the ventricular septum and ventricular septal defects, with applications for two-dimensional echocardiography. Mayo Clin Proc 60:741, 1985
119. Hilwig RW, Bishop SP. Anomalous pulmonary venous return in a Great Dane. Am J Vet Res 36:229, 1975
120. Hamlin RL, Smetzer DL, Smith CR. Interventricular septal defect (Roger's disease) in the dog. J Am Vet Med Assoc 145:331, 1964
121. Clark DR, Anderson JG, Paterson C. Imperforate cardiac septal defect in a dog. J Am Vet Med Assoc 156:1020, 1970
122. Breznock EM, Vasko JS, Hilwig RW, et al. Surgical correction, using hypothermia, of an interventricular septal defect in the dog. J Am Vet Med Assoc 158:1391, 1971
123. Breznock EM. Spontaneous closure of ventricular septal defects in the dog. J Am Vet Med Assoc 162:399, 1973
124. Gelatt KN, McGill LD. Clinical characteristics in microphthalmia with colobomas of the Australian shepherd dog. J Am Vet Med Assoc 162:393, 1973
125. Eyster GE, Whipple RD, Anderson LK, et al. Pulmonary artery banding for ventricular septal defect in dogs and cats. J Am Vet Med Assoc 170:434, 1977
126. Feldman EC, Nimmo-Wilkie JS, Pharr JW. Eisenmenger's syndrome in the dog: Case reports. J Am Anim Hosp Assoc 17:477, 1981
127. McCaw D, Aronson E. Congenital cardiac disease in dogs. [VII. Ventricular septal defect.] Mod Vet Prac 65:767, 1984
128. Nishida K, Wakao Y, Watanabe T, et al. A case of the Eisenmenger syndrome in a dog. J Jap Vet Med Assoc 41:263, 1988
129. Bellah JR, Spencer CP, Brown DJ, et al. Congenital cranioventral abdominal wall, caudal sternal, diaphragmatic, pericardial, and intracardiac defects in Cocker Spaniel littermates. J Am Vet Med Assoc 194:1741, 1989
130. Nakai M, Tomino T, Goto V, et al. Quantitative evaluation of the pattern of shunt flow in the right ventricle and pulmonary artery of dogs with experimental ventricular septal defect. J Clin Invest 72:779, 1983
131. Okubo S, Nakai M, Tomino T. Relevance of location of defect and pulmonary vascular resistance to the intracardiac pattern of left to right shunt flow in dogs with experimental ventricular septal defect. Circulation 73:775, 1986
132. Suter PF. The radiographic diagnosis of canine and feline heart disease. Comp Cont Educ Pract Vet 3:441, 1981
133. Nimmo-Wilkie JS, Feldman EC. Pulmonary vascular lesions associated with congenital heart defects in three dogs. J Am Anim Hosp Assoc 17:485, 1981
134. Braden TD, Appleford MD, Hartsfield SM. Correction of a ventricular septal defect in a dog. J Am Vet Med Assoc 161:507, 1994
135. Sheridan JP, Mann PH, Stock TE. Pulmonary artery banding in the cat: A case report. J Small Anim Pract 12:45, 1971
136. Lister G, Hellenbrand WE, Kleinman CS, et al. Physiologic effects of increasing hemoglobin concentration in left-to-right shunting in infants with ventricular septal defects. N Engl J Med 306:502, 1982
137. Synhorst DP, Laver RM, Doty DB, Brady MJ. Hemodynamic effects of vasodilator agents in dogs with experimental ventricular septal defects. Circulation 54:472, 1976
138. Knight DH, Patterson DF, Melbin J. Constriction of fetal ductus arteriosus induced by oxygen, acetylcholine, and norepinephrine in normal dogs and those genetically predisposed to persistent patency. Circulation 47:127, 1973
139. Gittenberger-de-Groot J, Strengers JL, Menlink M, et al. Histologic studies on normal and persistent ductus arteriosus in the dog. J Am Coll Cardiol 6:394, 1985
140. House EW, Ederstrom HE. Anatomical changes with age in the heart and ductus arteriosus in the dog after birth. Anat Rec 160:289, 1968
141. Reed JH, Bonasch H. The surgical treatment of a persistent right aortic arch and patent ductus arteriosus in a dog. Can Vet J 5:240, 1964

142. Buchanan JW, Soma LR, Patterson DF. Patent ductus arteriosus surgery in small dogs. J Am Vet Med Assoc 151:701, 1967
143. Buchanan JW. Symposium: Thoracic surgery in the dog and cat. III. Patent ductus arteriosus and persistent right aortic arch surgery in dogs. J Small Anim Pract 9:409, 1968
144. Breznock EM, Wisloh A, Hilwig RW, Hamlin RL. A surgical method for correction of patent ductus arteriosus in the dog. J Am Vet Med Assoc 158:753, 1971
145. Smetzer DL, Breznock EM. Auscultatory diagnosis of patent ductus arteriosus in the dog. J Am Vet Med Assoc 160:80, 1972
146. Cohen JS, Tilley LP, Liu SK, Dehoff WD. Patent ductus arteriosus in five cats. J Am Anim Hosp Assoc 11:95, 1975
147. Eyster GE, Whipple RD, Evans AT, et al. Recanalized patent ductus arteriosus in the dog. J Small Anim Pract 16:743, 1975
148. Eyster GE, Eupler JT, Cords GB, Johnston J. Patent ductus arteriosus in the dog: Characteristics of occurrence and results of surgery in one hundred consecutive cases. J Am Vet Med Assoc 168:435, 1976
149. Atwell RB. Patent ductus arteriosus in a dog—attempted medical closure. Vet Rec 101:425, 1977
150. Ackerman N, Burk R, Hahn AW, Hayes HM Jr. Patent ductus arteriosus in the dog: A retrospective study of radiographic, epidemiologic, and clinical findings. Am J Vet Res 39:1805, 1978
151. Jeraj K, Ogborn P, Lord PF, Wilson JW. Patent ductus arteriosus with pulmonary hypertension in a cat. J Am Vet Med Assoc 172:1432, 1978
152. Weirich WE, Blevins WE, Rebar AH. Late consequences of patent ductus arteriosus in the dog: A report of six cases. J Am Anim Hosp Assoc 14:40, 1978
153. Jones CL, Buchanan JW. Patent ductus arteriosus: Anatomy and surgery in a cat. J Am Vet Med Assoc 179:364, 1981
154. Pyle RL, Park RD, Alexander AF, Hill BL. Patent ductus arteriosus with pulmonary hypertension in the dog. J Am Vet Med Assoc 178:565, 1981
155. Aronson E, McCaw D. Patent ductus arteriosus. A common congenital defect [of dogs] that must be corrected surgically. Vet Med Rev USA 4:2, 1983
156. Deussen A, Heusch G, Schipke J, et al. Persistent ductus arteriosus in three German Shepherd dogs. Zentralbl Veterinarmed, A31:140, 1984
157. O'Brien SE, Riedesel EA, Myers RK, et al. Right-to-left patent ductus arteriosus with dysplastic left ventricle in a dog. J Am Vet Med Assoc 192:1435, 1988
158. Malik R, Turnbull GR, Black AP. Patent ductus arteriosus in five related female border collies. Aust Vet Pract 21:2, 1991
159. Patterson DF. Congenital defects of the cardiovascular system of dogs: Studies in comparative cardiology. Adv Vet Sci Comp Med 20:1, 1976
160. Brown DJ, Patterson DF. Pulmonary atresia with intact ventricular septum and agenesis of the ductus arteriosus in a pup. J Am Vet Med Assoc 195:229, 1989
161. Turk JR, Miller LM, Miller JB, Sande RD. Necrotizing pulmonary arteritis in a dog with patent ductus arteriosus. J Small Anim Pract 22:603, 1981
162. Will JW. Subvalvular pulmonary stenosis and aorticopulmonary septal defect in the cat. J Am Vet Med Assoc 154:913, 1969
163. Eyster GE, Dalley JB, Chaffee A, et al. Aorticopulmonary septal defect in a dog. J Am Vet Med Assoc 167:1094, 1975
164. Nelson AW. Aorticopulmonary window in a dog. J Am Vet Med Assoc 188:1055, 1986
165. Malik R, Bellenger CR, Hunt GB, et al. Aberrant branch of the bronchoesophageal artery mimicking patent ductus arteriosus in a dog. J Am Anim Hosp Assoc 30:162, 1994
166. Birchard SJ, Bonagura JD, Fingland RB. Results of ligation of patent ductus arteriosus in dogs: 201 cases (1969–1988). J Am Vet Med Assoc 196:2011, 1990
167. Henderson RA, Jackson WF. Modified double ligation and division of patent ductus arteriosus. *In* Bojrab M (ed). Current Techniques in Small Animal Surgery. Philadelphia, WB Saunders, 1990, p 501
168. Weirich WE. Conventional surgical correction of patent ductus arteriosus. *In* Bojrab M (ed). Current Techniques in Small Animal Surgery. Philadelphia, WB Saunders, 1990, p 507
169. Lloyd TR, Fedderly R, Mendelsohn AM, et al. Transcatheter occlusion of patent ductus arteriosus with Gianturco coils. Circulation 88:1412, 1993
169a. Grifka RG, Miller MW, Frischmeyer KJ, et al. Transcatheter occlusion of a patent ductus arteriosus in a Newfoundland puppy using the Gianturco-Grifka vascular occlusion device. J Vet Intern Med 10:42, 1996
169b. Fox PR, Bond B, Sommer R. Nonsurgical transcatheter coil occlusion of patent ductus arteriosus in two dogs using a preformed nitinol snare delivery technique. J Vet Int Med 12:182, 1998
170. Hamlin RL, Smith CR, Rudy RL, Nash PA. Antemortem diagnosis of tetralogy of Fallot in a dog. J Am Vet Med Assoc 140:948, 1962
171. Clark DR, Ross JN, Hamlin RL, Smith CR. Tetralogy of Fallot in the dog. J Am Vet Med Assoc 152:462, 1968
172. Bolton GR, Ettinger SJ, Liu SK. Tetralogy of Fallot in three cats. J Am Vet Med Assoc 160:1622, 1972
173. Kirby D, Gillick A. Polycythemia and tetralogy of Fallot in a cat. Can Vet J 15:114, 1974
174. Eyster GE, Weber W, McQuillan W. Tetralogy of Fallot in a cat. J Am Vet Med Assoc 171:280, 1977
175. Lombard CW, Twitchell MJ. Tetralogy of Fallot, persistent left cranial vena cava and retinal detachment in a cat. J Am Anim Hosp Assoc 14:624, 1978
176. Hawe RS, Witler WR, Wilson JB. Tetralogy of Fallot in a 5-year old cat. J Am Anim Hosp Assoc 15:329, 1979
177. VanHeerden J, Lourens DC. Tetralogy of Fallot in a two and one half year old cat. J Am Anim Hosp Assoc 17:129, 1981
178. Miller CW, Holmberg DL, Bowen V, et al. Microsurgical management of tetralogy of Fallot in a cat. J Am Vet Med Assoc 186:708, 1985
179. Herrtage ME, Hall LW, English TA. Surgical correction of the tetralogy of Fallot in a dog. J Small Anim Pract 24:51, 1983
180. Garson A, Gillette PC, McNamara DG. Propranolol: The preferred palliation for tetralogy of Fallot. Am J Cardiol 47:1098, 1981
181. Eyster GE, Anderson LK, Sawyer DC, et al. Beta-adrenergic blockades for management of tetralogy of Fallot in a dog. J Am Vet Med Assoc 169:637, 1976
182. Beekman RH, Tuuri DT. Acute hemodynamic effects of increasing hemoglobin concentration in children with a right to left ventricular shunt and relative anemia. J Am Coll Cardiol 5:357, 1985
183. Voncolditz JH, Coon RL, Clifford PS, et al. Effects of chronic right to left cardiac shunt on hypoxic sensitivity of mongrel dogs. J Appl Physiol 58:1767, 1985
184. Bonagura JD, Pipers FS. Diagnosis of cardiac lesions by contrast echocardiography. J Am Vet Med Assoc 182:396, 1983

185. Roberts WC. A simple histologic classification of pulmonary arterial hypertension. Am J Cardiol 58:385, 1986
186. Lord PF, Liu SK, Carmichael JA. Congenital tricuspid stenosis with right ventricular hypoplasia in a cat. J Am Vet Med Assoc 153:300, 1968
187. Jeraj K, Ogburn PN, Jessen CA, et al. Double outlet right ventricle in a cat. J Am Vet Med Assoc 173:1356, 1978
188. Turk JR, Miller LM, Hegreberg GA. Double outlet right ventricle in a dog. J Am Anim Hosp Assoc 17:789, 1981
189. Straw RC, Aronson EF, McCaw DL. Transposition of the great arteries in a cat. J Am Vet Med Assoc 187:634, 1985
190. Buergelt CD, Suter PPF, Kay WJ. Persistent truncus arteriosus in a cat. J Am Vet Med Assoc 153:548, 1968
191. Hamlin RL, Smetzer DL, Smith CR. Congenital mitral insufficiency in the dog. J Am Vet Med Assoc 146: 1088, 1965
192. Hamlin RL, Harris SG. Mitral incompetence in Great Dane pups. J Am Vet Med Assoc 154:790, 1969
193. Dear MG. Mitral incompetence in dogs of 0-5 years of age. J Small Anim Pract 12:1, 1971
194. Weirich WE, et al. Congenital tricuspid insufficiency in a dog. J Am Vet Med Assoc 162:1025, 1974
195. Liu SK, Tilley LP. Malformation of the canine mitral valve complex. J Am Vet Med Assoc 167:465, 1975
196. Liu SK, Tilley LP. Dysplasia of the tricuspid valve in the dog and cat. J Am Vet Med Assoc 169:625, 1976
197. Eyster GE, Anderson L, Evans AT. Ebstein's anomaly: A report of 3 cases in the dog. J Am Vet Med Assoc 170:709, 1977
198. Liu S, Brown B. Malformation of mitral valve complex associated with cardiac dysfunction in 120 cats. Lab Invest 58:1, 1988
199. DeMadron E, Kadish A, Spear JF, et al. Incessant atrial tachycardias in a dog with tricuspid dysplasia. J Vet Intern Med 1:163, 1987
200. Tilley LP, Liu SK. Letter to the editor. J Am Vet Med Assoc 17:798, 1977
201. Detweiler DK, Brodey RS, Glickinger GL. Diagnosis and surgical correction of peritoneopericardial diaphragmatic hernia. J Am Vet Med Assoc 137:177, 1960
202. Baker GJ, Williams CSF. Diaphragmatic pericardial hernia in the dog. Vet Rec 78:578, 1966
203. Atkins CE. Suspect congenital peritoneopericardial diaphragmatic hernia in an adult cat. J Am Vet Med Assoc 165:175, 1974
204. Evans SM, Biery DW. Congenital peritoneopericardial diaphragmatic hernia in the dog and cat: A literature review and 17 additional case histories. Vet Radiol 21:108, 1980
205. Willard MD, Aronson E. Peritoneopericardial diaphragmatic hernia in a cat. J Am Vet Med Assoc 178:481, 1981
206. Eyster GA, Evans AT, Blanchard GL, et al. Congenital pericardial diaphragmatic hernia and multiple cardiac defects in a litter of collies. J Am Vet Med Assoc 170:516, 1977
207. Van der Gaag I, VanDerLuer RJT. Eight cases of pericardial defects in the dog. Vet Pathol 14:14, 1977
208. Bellah JR, Whitton DL, Ellison GW, et al. Surgical correction of concomitant cranioventral abdominal wall, caudal sternal, diaphragmatic, and pericardial defects in young dogs. J Am Vet Med Assoc 195:1722, 1989
208a. Skrodski M, Allgoewer I, Grevel V. Die kongenitale peritoneoperikardiale Hernie bei 16 Katzen Teil 1: Literaturübersicht und Kasuistik. Kleintierpraxis 42:973, 1998
209. Sisson DD, Thomas WP, Reed J, et al. Intrapericardial cysts in the dog. J Vet Intern Med 7:364, 1993
210. Gordon B, Trautvetter E, Patterson DF. Pulmonary congestion associated with cor triatriatum in a cat. J Am Vet Med Assoc 180:75, 1982
211. Linde-Sipman JS, Stokhof AA. Triple atria in a pup. J Am Vet Med Assoc 165:539, 1974
212. Stern A, McClure RC, Holmberg D. Cor triatriatum dexter in a dog. Comp Cont Educ Pract Vet 8:401, 1986
213. Miller MW, Bonagura JD, Dibartola SP, et al. Budd-Chiari–like syndrome in two dogs. J Am Anim Hosp Assoc 25:277, 1989
214. Malik R, Hunt GB, Chard RB, et al. Congenital obstruction of the caudal vena cava in a dog. J Am Vet Med Assoc 197:880, 1990
215. Otto CM, Mahaffey M, Jacobs C, et al. Cor triatriatum dexter with Budd-Chiara syndrome and a review of ascites in young dogs. J Small Anim Pract 31:385, 1990
216. Jevens DJ, Johnston SA, Jones CA, et al. Cor triatriatum dexter in two dogs. J Am Anim Hosp Assoc 29:289, 1993
217. Alboliras ET, Edwards WD, Driscoll DJ, et al. Cor triatriatum dexter: Two-dimensional echocardiographic diagnosis. J Am Coll Cardiol 9:334, 1994
218. Kaufman AC, Swalec KM, Mahaffey MB. Surgical correction of cor triatriatum dexter in a puppy. J Am Anim Hosp Assoc 30:157, 1994
219. Paasch LH, Zook BC. The pathogenesis of endocardial fibroelastosis in Burmese cats. Lab Invest 42:197, 1980
220. Krahwinkel DJ, Coogan PS. Endocardial fibroelastosis in a Great Dane pup. J Am Vet Med Assoc 159:327, 1971
221. Lombard CW, Buergelt CD. Endocardial fibroelastosis in four dogs. J Am Anim Hosp Assoc 20:271, 1984
222. Hawe RS, Tyler DE, Latimer KS. Congenital unilateral absence of a pulmonary artery in a cat. J Am Anim Hosp Assoc 21:111, 1985
223. Kealy JK. Persistent right aortic arch in the Greyhound. Irish Vet J 15:197, 1961
224. Imhoff RK, Foster WJ. Persistent right aortic arch in a ten year-old dog. J Am Vet Med Assoc 143:599, 1963
225. Coward TG. Persistent right aortic arch in two Great Dane littermates. J Small Anim Pract 5:245, 1964
226. Lawson DD, Pirie HM. Conditions of the canine oesophagus—II. Vascular rings, achalasia, tumours and peri-oesophageal lesions. J Small Anim Pract 7:117, 1966
227. Van der Ingh TSG, Van der Line–Sipman JS. Vascular rings in the dog. J Am Vet Med Assoc 164:939, 1974
228. Helphrey ML. Vascular ring anomalies in the dog. Vet Clin North Am (Small Anim Pract) 9:207, 1979
229. Aultman SH, Chambers JN, Vestre WA. Double aortic arch and persistent right aortic arch in two littermates: Surgical treatment. J Am Anim Hosp Assoc 16:533, 1980
230. Martin DG, Ferguson EW. Double aortic arch in a dog. J Am Vet Med Assoc 183:697, 1983
231. McCandlish IA, Nash AS, Peggram A. Unusual vascular ring in a cat: Left aortic arch with right ligamentum arteriosum. Vet Rec 114:338, 1984
232. Berry AP, Brouwer GJ, Tennant BJ. Persistent right aortic arch in a kitten. Vet Rec 114:336, 1984
233. Wheaton LG, Blevins WE, Weirich WE. Persistent right aortic arch associated with other vascular anomalies in two cats. J Am Vet Med Assoc 184:848, 1984
234. Hurley K, Miller MW, Willard MD, et al. Left aortic arch and right ligamentum arteriosum causing esophageal obstruction in a dog. J Am Vet Med Assoc 203:410, 1993
235. Shires PK, Liu W. Persistent right aortic arch in dogs: A long-term follow-up after surgical correction. J Am Anim Hosp Assoc 17:773, 1994

235a. Muldoon MM, Birchard SJ, Ellison GW. Long-term results of surgical correction of persistent right aortic arch in dogs: 25 cases (1980–1995). J Am Vet Med Assoc 210:1761, 1997
236. Lombard CW, Knight DH, Buchanan JW, Riffle RA. Clinico-pathologic conference. J Am Vet Med Assoc 172:75, 1978
237. Scotti C, Galloni M. Left anterior vena cava in a dog. Veterinari Cremona 3:11, 1989
238. Wallace CR. Absence of posterior vena cava in a dog. J Am Vet Med Assoc 136:27, 1960
239. Salmeri KR, Bellah JR, Ackerman N, et al. Unilateral congenital aneurysm of the jugular, linguofacial, and maxillary veins in a dog. J Am Vet Med Assoc 198:651, 1991
240. Sammarco CD, Regan J, Ward CR, Buchanan JD. Caudal venous return through a left azygos vein in a dog. Vet Radiol Ultrasound 36:517, 1995

25

Acquired Valvular Heart Disease in Dogs and Cats

DAVID SISSON

CLARENCE KVART

PETER G. G. DARKE

CHRONIC DEGENERATIVE VALVULAR DISEASE

MITRAL REGURGITATION

Chronic degenerative valvular disease (CDVD) is the most common cause of cardiac disability in dogs. As many as three fourths of all dogs with signs of congestive heart failure suffer from mitral regurgitation caused by myxomatous degeneration of the valve leaflets or chordae tendineae.[1-5] The mitral valve is affected either alone or together with the tricuspid valve in most dogs. Insufficiency of the mitral valve can also develop secondary to myocardial disease and other cardiac disorders, causing volume overload of the left side of the heart. In these circumstances, valvular insufficiency results from the combined effects of chamber dilatation, enlargement of the mitral annulus, and ventricular or papillary muscle dysfunction. Accordingly, dogs with a patent ductus arteriosus or dilated cardiomyopathy often develop mild to moderate mitral regurgitation.

Less is known about the prevalence and causes of valvular diseases in cats, in which mitral regurgitation usually occurs in association with some form of myocardial disease. Tashjian and associates reported just 7 cases of mitral valvular fibrosis and 2 cases of tricuspid valvular fibrosis in 202 consecutively performed necropsies.[6] Necropsy studies of 112 cats with heart failure from acquired causes revealed mitral valvular fibrosis in 39 cats, papillary muscle fibrosis in 50, and fused chordae tendineae in 17.[7] In this and subsequent publications, the importance of the accompanying myocardial lesions was emphasized, obscuring the significance of the valvular changes.[7-11] More recently, Harpster reported mitral insufficiency in 75 of 500 cats (15 percent), but he did not specify the nature of the disease process or the technique used to make this determination.[12]

Inasmuch as many cats are presented in end-stage heart failure, the precise relationship between mitral regurgitation and coexisting myocardial disease is uncertain. In cats with hypertrophic cardiomyopathy, mitral regurgitation and fibrosis of the anterior mitral valve leaflet occur as unavoidable consequences of dynamic left ventricular outflow tract (LVOT) obstruction. Mitral regurgitation also occurs in many cats with endomyocarditis and restrictive

myocardial disease, in which the mitral valve leaflets, chordae tendineae, and papillary muscles are often found to be distorted by adhesions and fibrotic plaques (chapter 28). Congenital mitral valve malformations can cause valvular stenosis, insufficiency, or dynamic LVOT obstruction.

ANATOMY OF THE MITRAL VALVE COMPLEX

GROSS ANATOMY. Proper closure of the mitral valve requires the integrated action of the six anatomic components that define the mitral valve apparatus: (1) the mitral leaflets, (2) the chordae tendineae, (3) the mitral annulus, (4) the left atrial wall, (5) the papillary muscles, and (6) the left ventricular wall.[13, 14] The anatomy of the mitral valve is similar in humans, dogs, and cats (see Figs. 2–5, 2–6).[15, 16] Two main cusps of the mitral valve can usually be identified: a large anterior (septal, or aortic) cusp and a smaller posterior (parietal or mural) cusp.[15, 17] The anterior cusp divides the base of the left ventricle into an inflow region that receives blood from the left atrium and an outflow region through which blood is expelled. The bases of the aortic and mural cusps form approximately one half the circumference of the atrioventricular ring, with commissural cusp tissue completing the encirclement of the mitral orifice.[17]

The tips and midventricular surface of the valve cusps are anchored to two main papillary muscles by first- and second-order chordae tendineae, respectively.[4, 15] Third-order chordae tendineae can be identified extending from the posterior and commissural cusps directly to the ventricular wall. Third-order chordae tendineae are not normally found on the anterior cusp of the mitral valve.[15]

HISTOLOGIC ANATOMY. Histologic examination of a normal mitral valve leaflet reveals four distinctive layers.[4, 13] The *atrialis* consists of a thin layer of endothelial cells supported by a framework of connective tissue and a thin layer of smooth muscle. Beneath the atrialis is the *spongiosa,* a loose collection of collagen, fibroblasts, Anitschkow cells, and elastic fibers embedded in a mucopolysaccharide-rich ground substance. The *fibrosa* consists of a dense layer of compact collagen that is continuous with similar tissue in the mitral annulus and the central core of the chordae tendineae.[13] The ventricular surface of the valve is lined by the *ventricularis,* which is structurally similar to the atrialis except that it lacks a distinct layer of smooth muscle. Vascular structures and myocardial tissue are present only in the basilar one third of the mitral valve. These tissues extend from the left atrial wall to a location just beneath the atrialis.[13, 18–21]

The chordae tendineae are composed of a central core of collagen that is arranged parallel to the long axis of the chordae.[13] The dense, collagenous core is surrounded by a loose mesh of collagen, elastic fibers, and ground substance, which in turn is enveloped by an encircling layer of endothelial cells.

NORMAL FUNCTION OF THE MITRAL VALVE COMPLEX

The exact mechanism of mitral valve closure is uncertain and probably varies in differing circumstances. Each component of the mitral valve apparatus contributes to valve closure.[14, 16, 22, 23] The left atrium plays an important role during the initial phases of mitral valve closure. As a consequence of left atrial systole, blood accelerates through the mitral orifice, creating an area of negative pressure within the inflow tract, drawing the mitral valve leaflets together. Eddy currents propagated in the left ventricle aid early valve closure by pushing the leaflets together. Atrial relaxation initiates reversal of the atrioventricular pressure gradient, contributing to early valve closure. Interruption of the coordinated sequential activation of the atrium and ventricle, as occurs with atrioventricular dissociation, can produce mild mitral regurgitation.

Activation of the papillary muscles at the onset of ventricular systole draws the mitral leaflets downward and together. Mitral regurgitation is often observed when the sequence of activation of the papillary muscles and the left ventricular wall is altered, as occurs with ventricular ectopic beats or ventricular asynergy from any cause. As systole proceeds, rising pressure within the ventricle results in firm coaptation of the valve leaflets. The tendency of the valve leaflets to evert into the atrium during ventricular systole is opposed by the chordae tendineae, the papillary muscles, and the buttressing action of the coapted valve leaflets.[24] As the ventricle contracts, constriction of the mitral annulus reduces the area the mitral leaflets must bridge.

The functional interdependence of the various components of the mitral valve complex is best illustrated by the observation that valvular insufficiency caused by failure of any one of these structures results in progressive valvular incompetence from the induced malfunction of the remaining elements. Damage to the valvular tissue or the supporting chordae tendineae, resulting in valvular insufficiency, induces left atrial and left ventricular enlargement and mitral annulus dilatation. These changes cause malalignment of the papillary muscles, causing a further increase in the regurgitant volume. By these mechanisms, progressive enlargement of the left side of the heart and dilation of the mitral annulus establish a never-ending cycle of worsening disease ("mitral regurgitation begets mitral regurgitation").[25]

PATHOLOGY OF CHRONIC VALVULAR DISEASE IN DOGS

Myxomatous degeneration best describes the histologic valve changes in dogs with chronic degenerative valvu-

lar disease, or CDVD[4] (also termed *endocardiosis*) (chapter 37). Similar changes are reported in humans with the mitral valve prolapse syndrome and in patients experiencing spontaneous rupture of a chorda.[26–30] The progression of CDVD in dogs, once referred to as warty valve disease, has been most thoroughly described by Whitney,[31] Buchanan,[4] and Kogure.[32]

The earliest changes, designated as type I lesions, consist of a few small, discrete areas of opacity or nodules in the area of valvular apposition opposite the site of origin of the chordae tendineae. In type II lesions, the nodules have become larger and more numerous and have started to coalesce. The chordae tendineae are usually unaffected at this stage, and clinical evidence of valvular regurgitation is generally lacking. Type III lesions are characterized by large nodules or plaquelike deformities resulting from the further coalescence of lesions. The chordae tendineae are thickened where they attach to the valve leaflet. At this stage, the valve has become noticeably thickened and is less flexible than normal.[4] The basal portion of the valve is now affected, and areas of calcification and hemorrhage may be observed within the valve stroma. Valvular insufficiency is often present at this stage. In dogs with type IV lesions, the valve cusps are contracted and grossly distorted. The free valve edges may be rolled upward; chordae tendineae are thickened proximally, are often elongated, and are occasionally ruptured. At this stage of the disease the valve may be described as "ballooning," "parachute-like," or as "billowing sails,"[4] and valvular insufficiency is usually present (Fig. 25–1).

It is important to recognize that these pathologic changes are not confined to the mitral valve. Buchanan reported the incidence of valve involvement in dogs with chronic valvular disease as follows: mitral valve alone, 62 percent; mitral and tricuspid valves, 32.5 percent; mitral and aortic valves, 2.5 percent; tricuspid valve alone, 1.3 percent; and aortic valve alone, 1.3 percent.[4] Similar findings have been reported by others.[1–3, 32–37]

The prevalence and severity of myxomatous degeneration lesions increase with advancing age.[1–4, 32–37] Early valve lesions, consisting mainly of proliferations of the endothelium and of the underlying fibroelastic tissue in areas of valvular contact, cannot be distinguished from normal aging changes. Type I and type II lesions are compatible with normal aging except that they occur at an inappropriately early period of life.[4, 37–41] In type III and type IV lesions, the most prominent histologic features include degeneration of the fibrosa and thickening of the spongiosa. Collagen bundles in the fibrosa lose their cross-striations, become hyalinized and disorganized, and may disintegrate and disappear.[4] Acid mucopolysaccharides accumulate within the fibrosa, displacing fragments of disrupted collagen into the central portion of the dystrophic valve. The spongiosa becomes tremendously thickened as a result of edema and accumulations of the acid mucopolysaccharides, hyaluronic acid and chondroitin sulfate.[42–47] As the lesions progress, the distinction between the spongiosa and fibrosa becomes difficult to make.

Other morphologic changes reported in dogs with mitral regurgitation include left atrial dilatation, dilatation of the mitral annulus, and eccentric hypertrophy of the left ventricle.[4] Jet impact lesions, Zahn-Schmincke patches, and endomyocardial tears are observed in the left atrium of some affected dogs.[4, 33] Substantial lipid[46] and amyloid accumulations are present in the valves of some dogs.[48, 49] Intramural coronary arteriosclerosis and focal myocardial fibrosis are common in dogs with chronic valvular disease.[33, 50] These lesions may be due to vascular remodeling induced by angiotensin II.

ETIOLOGY OF CHRONIC DEGENERATIVE VALVULAR DISEASE (MYXOMATOUS VALVULAR DEGENERATION)

The etiology of chronic degenerative valvular disease (CDVD) has not been ascertained. Some investigators believe that collagen dissolution is the basic pathologic process responsible for myxomatous degeneration (MXD), and the term "dyscollagenosis" was coined to describe this proposed pathologic process.[51] Buchanan[4] suggested that a genetically influenced degeneration of collagen might be responsible for MXD in dogs. This attractive theory is supported by the observations that chondrodystrophic breeds are predisposed to CDVD, and these same breeds are also predisposed to other connective tissue–related disorders such as intervertebral disc disease, ruptured cruciate ligaments, collapsing airways, and periodontal disease.

Collagen metabolism is a balance between synthesis and lysis, and both processes are regulated by a number of modifying influences. It is not known whether collagen dissolution in degenerative valve disease results from a primary disorder of collagen synthesis, collagen content, organization of collagen (arrangement of fibers), or abnormal collagenase activities. Over 275 different mutations in the genes for types I, II, III, IX, X, and XI collagens have been identified in humans.[52] Most of the mutations involve a single base, thereby changing the codon of a critical amino acid. Most of the amino acid substitutions are those of a bulkier amino acid for the obligatory glycine of the repeating Gly-X-Y sequence of the collagen triple helix. The valves of the heart are composed mainly of type I and type III collagen.[53] Defects of type I or type III collagen have been identified in human patients with chondrodysplasia, mitral valve prolapse, and Ehlers-Danlos syndrome.[54–56] Accumulations of procollagen have been measured in human patients with MXD

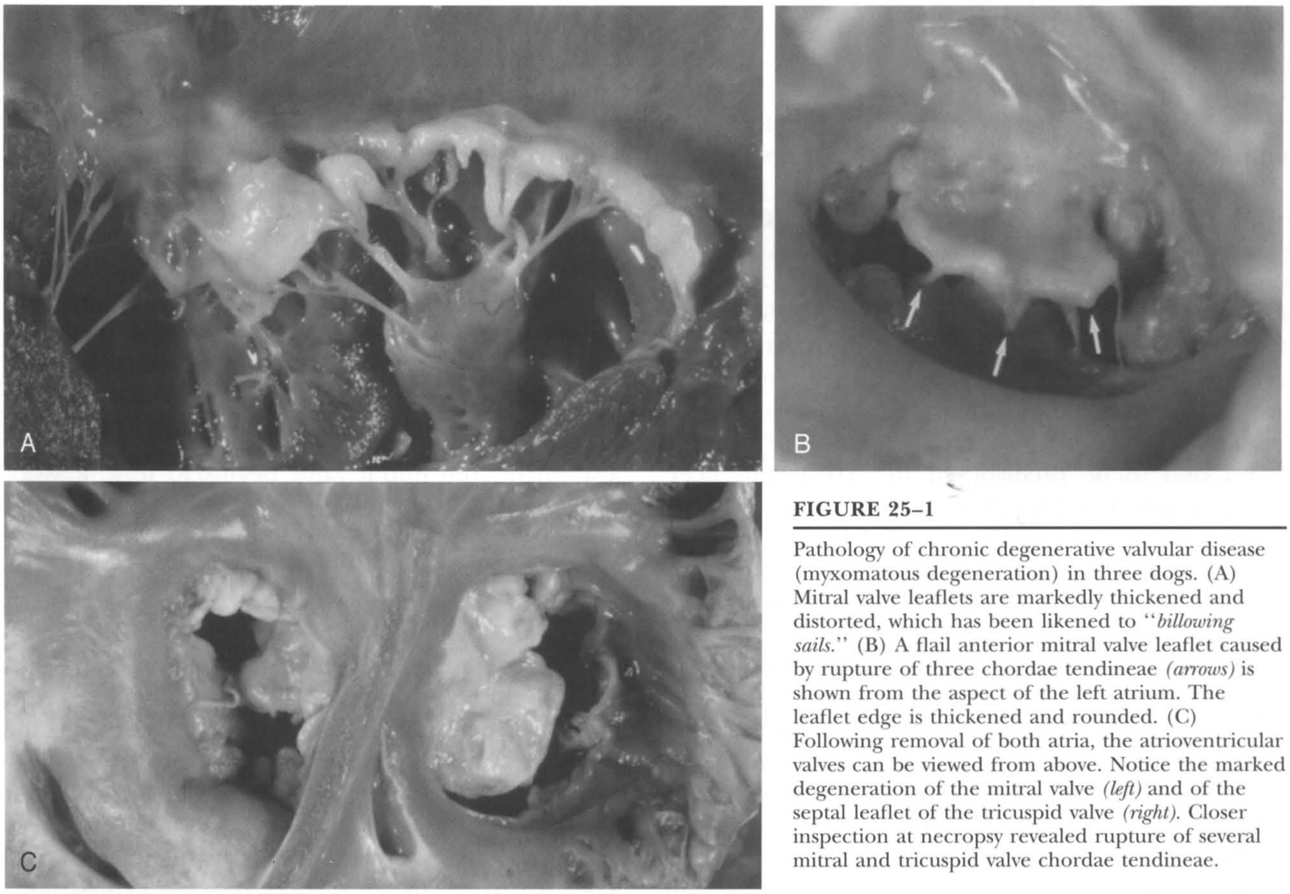


FIGURE 25–1

Pathology of chronic degenerative valvular disease (myxomatous degeneration) in three dogs. (A) Mitral valve leaflets are markedly thickened and distorted, which has been likened to "*billowing sails*." (B) A flail anterior mitral valve leaflet caused by rupture of three chordae tendineae *(arrows)* is shown from the aspect of the left atrium. The leaflet edge is thickened and rounded. (C) Following removal of both atria, the atrioventricular valves can be viewed from above. Notice the marked degeneration of the mitral valve *(left)* and of the septal leaflet of the tricuspid valve *(right)*. Closer inspection at necropsy revealed rupture of several mitral and tricuspid valve chordae tendineae.

associated with mitral valve prolapse, but this finding may simply indicate the production of new collagen as part of an attempted repair process.[57, 58] As yet, no one has identified a specific collagen abnormality in dogs with valvular MXD.

Increased enzymatic lysis of collagen and elastin has been proposed as a cause of myxomatous degeneration of the heart valves and as a cause of ruptured chordae tendineae in humans.[59, 60] Recent studies of other connective tissue diseases suggest a possible pathogenic role for one or several different matrix metalloproteinases (MMP).[61] Collagen lysis can be induced by excessive tissue activity of MMP 1 (collagenase).[62] This enzyme is regulated, in part, by the naturally occurring tissue inhibitor of MMP 1, referred to as TIMP-1. Others have suggested that excessive production of proteoglycans is the primary biochemical defect in dogs with CDVD.[63] According to this hypothesis, large accumulations of proteoglycans interfere with the normal assembly of collagen and elastin fibers. Mitral valve prolapse also occurs in Marfan's syndrome patients. Etiology involves mutations in the fibrillin-1 gene, a constituent of the microfibrillar scaffolding required for the assembly of elastic fibers.[64]

Other proposed causes of chronic valvular disease in dogs include stress, hypertension, hypoxia, prior viral or bacterial infection, and a variety of endocrine abnormalities.[4] There is little evidence to support the hypotheses that prior bacterial infection or immune-mediated phenomena play a substantial role in the disease process. Several investigators have suggested a link between hyperadrenocorticism and MXD.[4, 65] Experimental studies in dogs suggest that stress (ACTH, cortisol) can induce lesions morphologically similar to those of MXD.[66] In cultured human fibroblasts, dexamethasone treatment decreases synthesis of procollagen and causes down regulation of TIMP-1 synthesis, tilting the balance of collagen metabolism away from accumulation.[67] Tissue growth factor-beta has the opposite effect as it stimulates the synthesis of procollagen and TIMP-1. Angiotensin II and aldosterone also stimulate collagen synthesis, while angiotensin II additionally inhibits MMP-1 activity, the key enzyme for degradation of fibrillar collagen in the cardiac interstitium.[68] The increased incidence and severity of MXD in male dogs supports a role for other hormonal influences on CDVD as well.[4] The significance of the amyloid deposits in the valves of a small percentage (5 percent) of dogs with CDVD is unknown.[4, 48, 49] The pathology and pathogenic mechanisms of acquired valvular disease in cats have not been characterized.[5–7, 69]

EPIDEMIOLOGY OF CHRONIC DEGENERATIVE VALVULAR DISEASE

In the 1960s, the prevalence of CDVD, determined clinically in a diverse population of dogs presented to a teaching hospital in the United States, was reported to be 8.3 percent.[1, 2] The prevalence of CDVD was shown to increase with advancing age, so that approximately 10 percent of dogs 5 to 8 years old, 20 to 25 percent of dogs 9 to 12 years old, and 30 to 35 percent of dogs over 13 years old exhibited murmurs.[2] Small breed dogs, such as toy and miniature poodles, miniature schnauzers, Pomeranians, Chihuahuas, cocker spaniels, Pekingese, fox terriers, and Boston terriers, were found to be predisposed to CDVD; and male dogs were affected more frequently than female dogs (1.5 to 1.0 male to female ratio).[1, 2, 4] Other investigators reported prevalence data for CDVD ranging from 11 to 42 percent.[3, 34, 35, 37, 70] Many of these studies reported the prevalence of degenerative valve changes at necropsy rather than the clinical prevalence of valvular insufficiency.

Recent epidemiologic studies of CDVD, conducted mainly in the United Kingdom and Sweden, have focused on the cavalier King Charles spaniel breed. A high prevalence of mitral regurgitation in this breed was first reported in 1985 by Thrusfield and colleagues.[71] Soon thereafter, Darke[72] reported that cardiac murmurs were present in 59 percent of cavaliers 4 years of age and older, based on physical examinations performed at dog shows. In Sweden, which has a population of cavalier King Charles spaniels almost entirely emanating from the United Kingdom, cardiac murmurs were detected in 42 percent of dogs 4 years of age or older.[73] Echocardiographic examination of 150 cavaliers with heart murmurs confirmed that chronic valvular disease is the dominant cause of murmurs in the breed (Kvart C, Häggström J. Unpublished data).

The percentage of cavalier King Charles spaniels with a heart murmur was shown to depend on the age distribution of the dogs examined.[73] If a group of very young cavaliers is examined, a low prevalence of murmurs will be found, whereas a group of older dogs will have a very high prevalence of murmurs. The cumulative frequency of heart murmurs in relation to age groups is shown in Figure 25–2. From these data, approximately 50 percent of 7.5-year-old cavaliers would be expected to have a heart murmur. In a group of 10-year-old cavaliers, 85 percent would have murmurs. One study of 61 randomly selected cavaliers (mean age of 6.4±2.8 [SD] years) revealed that 52 percent had heart murmurs. In a 1993 study performed in the United States, Beardow and Buchanan[74] reported that 56 percent of cavaliers over 4 years of age and 100 percent of those 10 years old or older had murmurs. A lower prevalence was reported from a smaller survey in Australia.[75] The age-adjusted prevalence of mitral regurgitation in different age groups of cavaliers, based on surveys conducted in the United Kingdom, Sweden, Australia, and the United States, is shown in Figure 25–3. Clearly, the prevalence of chronic valvular disease in a given population depends on breed popularity and the age distribution of the dogs in that population.

PATHOPHYSIOLOGY OF MITRAL REGURGITATION

During the early stages of myxomatous degeneration, the mitral valve remains competent, no murmur is present, and no hemodynamic alterations occur. Eventually, the mitral valve begins to leak, a systolic murmur develops, and an increasing percentage of left ventricular output is ejected into the left atrium. The tendency for forward output to decline is compensated for by the Starling, renal, and neurohormonal mechanisms, and by eccentric hypertrophy of the left ventricle (chapters 3, 11). These compensatory processes are able to maintain normal cardiac output for a long period of time, often months or years, even when the regurgitant volume is large.[1, 2, 4] Decompression of the left ventricle into the low-pressure left atrium results in rapidly declining left ventricular wall tension and an increase in the velocity and extent of myocardial fiber shortening.[76, 77] Myocardial oxygen consumption rises only modestly as it is determined mainly by heart rate, contractility, and myocardial wall tension and is little affected by the increased work accomplished by fiber shortening.[78–81]

DETERMINANTS OF REGURGITANT VOLUME. As described by Gorlin's hydraulic equation, the volume of mitral regurgitant flow depends on the regurgitant orifice area (ROA), the pressure gradient between the left atrium (LA) and the left ventricle (LV), and the duration of systole.[82–84] Of these factors, ROA is quantitatively most important. The size of the regurgitant orifice depends on the severity of valve damage, the integrity of the chordae tendineae, and the combined effects of left atrial dilatation, annular dilatation, and ventricular dilatation on valvular function. The LV-LA pressure gradient and ROA are dynamic quantities that change as systole proceeds.[85] The ROA tends to decrease as LV diameter gets smaller. Increased preload or afterload and decreased myocardial contractility increase regurgitant volume as they increase LV size and ROA over the systolic time interval.[82, 84, 85] Diuretics and venodilators decrease LV size and the regurgitant orifice at the onset of systole. Arterial vasodilators and positive inotropic drugs increase the rate of myocardial fiber shortening, causing the LV dimensions and ROA to decrease at a faster rate. These effects have been convincingly and elegantly demonstrated in dogs with experimentally induced mitral regurgitation.[62, 63, 85–87]

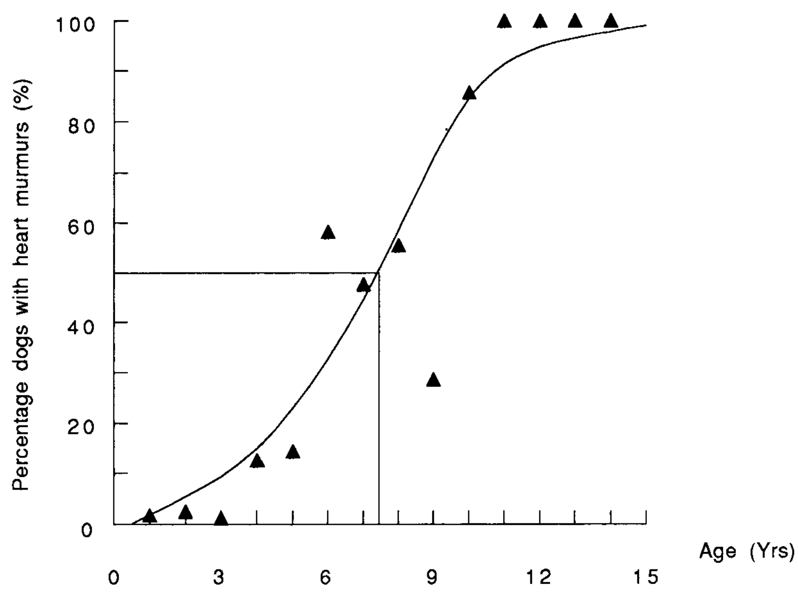


FIGURE 25-2

Estimation of the age at which 50% of cavalier King Charles spaniels have developed heart murmurs. *Solid line* shows the estimated cumulative function of heart murmurs by age. Points show the percentage of dogs with detected heart murmurs in different age groups from 494 examined Swedish cavalier King Charles spaniels. (From Häggström J, Hansson K, Kvart C, et al. Chronic valvular disease in the cavalier King Charles spaniel in Sweden. Vet Rec 131:549, 1992.)

Since the mitral regurgitant orifice and root of the aorta are in parallel, the ratio of forward blood flow to regurgitant flow depends on the ratio of aortic impedance to regurgitant impedance.[88] Increased systemic arteriolar resistance results in diminution of forward flow and causes regurgitant flow into the left atrium to increase. Conversely, the administration of arteriolar vasodilators decreases the volume of regurgitant flow independent of any change in the mitral regurgitant orifice.[88] Thus, there are two mechanisms of action for the vasodilating drugs: (1) reduction in ROA as a consequence of reduced ventricular size, and (2) reduction of the systolic LV-LA pressure gradient as a consequence of reduced aortic impedance. The first mechanism predominates in experimental models[82, 87, 88] of acute mitral regurgitation, but the relative importance of these mechanisms could differ in dogs with more chronic disease.

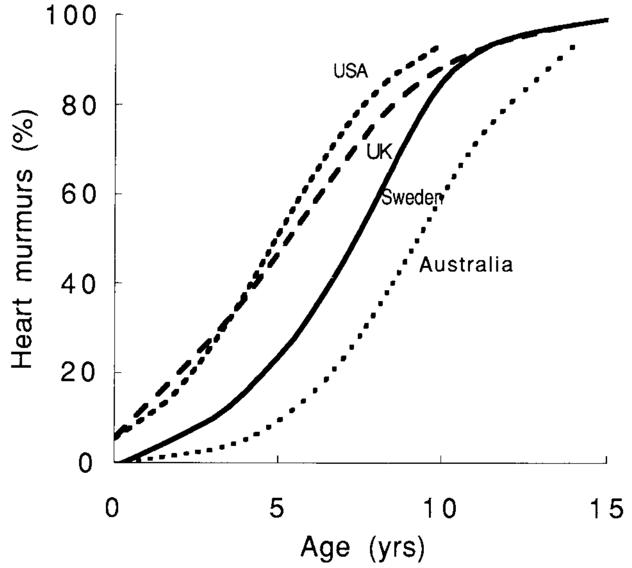


FIGURE 25-3

Estimation of the age at which 50% of cavalier King Charles spaniels have developed heart murmurs. *Solid lines* show the estimated cumulative functions of heart murmurs by age from studies in the United Kingdom (UK), Australia, Sweden, and USA. The investigation in the UK, Sweden, and USA is based on sufficient numbers of observations, whereas more cases need to be recorded in the older age group in Australia. (From Häggström J, Hansson K, Kvart C, et al. Chronic valvular disease in the cavalier King Charles spaniel in Sweden. Vet Rec 131:549, 1992.)

LEFT ATRIAL COMPLIANCE. When left atrial pressure rises sufficiently, pulmonary congestion develops, accompanied by the usual signs of left-sided congestive heart failure (CHF). Mean left atrial pressure is dependent on (1) the volume of regurgitant flow, (2) the output of the right side of the heart, (3) left ventricular diastolic pressure, and (4) the compliance of the left atrium.[76] Severe pulmonary congestion is most likely to develop when left atrial compliance is low and the regurgitant orifice is large.[76, 89] These conditions are present when a previously compensated patient suffers sudden rupture of a chordae tendineae. When severe mitral regurgitation develops over a long period of time, the dilated left atrial chamber becomes more compliant, buffering the pressure rise in the atrium as it compensates to provide an adequate ventricular filling volume. As a result, left atrial pressure may be only slightly elevated even in the face of massive regurgitant volumes. Left atrial pressure is also dependent on myocardial contractility and left ventricular compliance. When contractility declines in patients with CDVD, signs of pulmonary congestion are usually already evident.

ATRIOVENTRICULAR COUPLING. Cardiac performance in dogs with mitral regurgitation is extremely dependent on the optimized preload provided by an appro-

priately timed "atrial kick." During chronic mitral regurgitation, the left atrium enlarges in size and mass as it develops a more powerful booster action.[90] Loss of this augmented booster pump action can be catastrophic in dogs with severe mitral regurgitation. Atrial fibrillation in dogs with severe mitral regurgitation is usually heralded by sudden cardiac decompensation and the development of pulmonary congestion and signs of low cardiac output. The consequences of atrial fibrillation in dogs with experimentally induced mitral regurgitation include a 15 to 39 percent decline in cardiac output, a 22 to 65 percent fall in stroke volume, and a 2.5 to 9.5 mmHg increase in pulmonary capillary wedge pressure.[91] Maintenance of sinus rhythm should be a high priority in the management of dogs with mitral regurgitation.

NEUROHORMONAL RESPONSES. Moderate to severe heart failure in dogs with experimentally created or naturally occurring mitral regurgitation is accompanied by increased sympathetic nervous system activity and activation of the renin-angiotensin-aldosterone (R-A-A) system.[92, 93] Diuretic treatment further intensifies the activity of the R-A-A system.[92] Activation of plasma and tissue R-A-A systems stimulates expansion of the plasma volume, increases preload and afterload, and induces remodeling of vascular and myocardial tissues. A positive feedback loop is established in which mitral regurgitation results in progressive ventricular enlargement and declining cardiac performance; this, in turn, leads to increasingly severe mitral regurgitation.

The precise sequence and extent of neurohormonal activation in the early stages of degenerative valvular disease has not yet been clearly elucidated. In part, this is due to technical difficulties in obtaining accurate measurements of the resting plasma concentrations of these episodically released hormones.[94–98] Pedersen and colleagues found increased plasma renin activity and elevated concentrations of aldosterone in asymptomatic and mildly symptomatic cavaliers with CDVD.[95, 96] In apparent contradiction, Swedish investigators reported the findings of low plasma concentrations of angiotensin II and aldosterone in cavalier dogs with CDVD 1 year before, 1 to 6 months before, and at the onset of interstitial pulmonary edema (mild CHF, Fig. 25–4).[97] Based on these studies, they concluded that fluid retention in the early stages of developing heart failure may not be caused by activation of the plasma R-A-A system and that other mechanisms may be responsible for early sodium and water retention in dogs with mitral regurgitation.[97, 98] They further hypothesized that increased circulating concentrations of the atrial natriuretic peptide (ANP) effectively suppress the plasma R-A-A system in dogs with early, compensated CDVD. Several studies have confirmed that plasma concentrations of ANP and N-terminal pro-atrial natriuretic peptide (NT-proANP) are elevated in dogs with mitral regurgitation prior to the development of overt congestive heart failure.[98, 99] Further research is needed to determine the nature, extent, and clinical relevance of neurohormonal activation in dogs with early, compensated mitral insufficiency.

MYOCARDIAL CONTRACTILITY. In humans with mitral regurgitation, myocardial contractility is assessed primarily to determine the advisability of mitral valve replacement.[89, 100–104] Preoperative myocardial contractility has been shown to be an important determinant of left-sided heart function postoperatively, and it is of substantial value in predicting the surgical outcome. The assessment of myocardial contractility in dogs with mitral regurgitation has also received considerable attention, despite the fact that reparative surgery is rarely performed.[5, 105] Such data have been mainly used to argue for or against the use of positive inotropic drugs (digoxin) in dogs with mitral regurgitation.

The medical treatment of dogs with mitral regurgitation is not based on or determined by echocardiographic measures of myocardial contractility for several reasons. First, the ability of inotropic drugs to reduce regurgitant volume is not predicated on the status of myocardial contractility. Regurgitant volume decreases with positive inotropic treatment, even when myocardial contractility is normal.[82] Second, intrinsic myocardial contractility is very difficult to measure in dogs with mitral regurgitation. In dogs with chronic mitral regurgitation, myocardial contractility decreases slowly, but progressively and inexorably.[5, 106–110] This decline in contractility has been termed the *cardiomyopathy of volume overload* (see Fig. 33–1).[111] As a final consideration, the only positive inotropic agent currently available for chronic oral therapy is digoxin, which is a relatively weak positive inotrope. Treatment responses to digoxin are often attributed to its pronounced modulating influence on the autonomic nervous system or to other extracardiac effects (chapter 12).

Several factors unique to the condition of mitral regurgitation tend to obscure any decline in myocardial contractility. Traditional measurements used to describe ventricular function in other cardiac disorders, such as dilated cardiomyopathy, are not valid in patients with mitral regurgitation.[76] The ejection phase indices (ejection fraction, shortening fraction, mean velocity of circumferential fiber shortening) are increased relative to the true level of myocardial contractility, in part because of the unique loading conditions present in mitral insufficiency. Fiber shortening in dogs with mitral regurgitation is greatly augmented by increased preload (the Frank-Starling mechanism) and by reduced afterload (ventricular ejection into a low-pressure reservoir, the atria).

Myocardial contractility can be accurately assessed

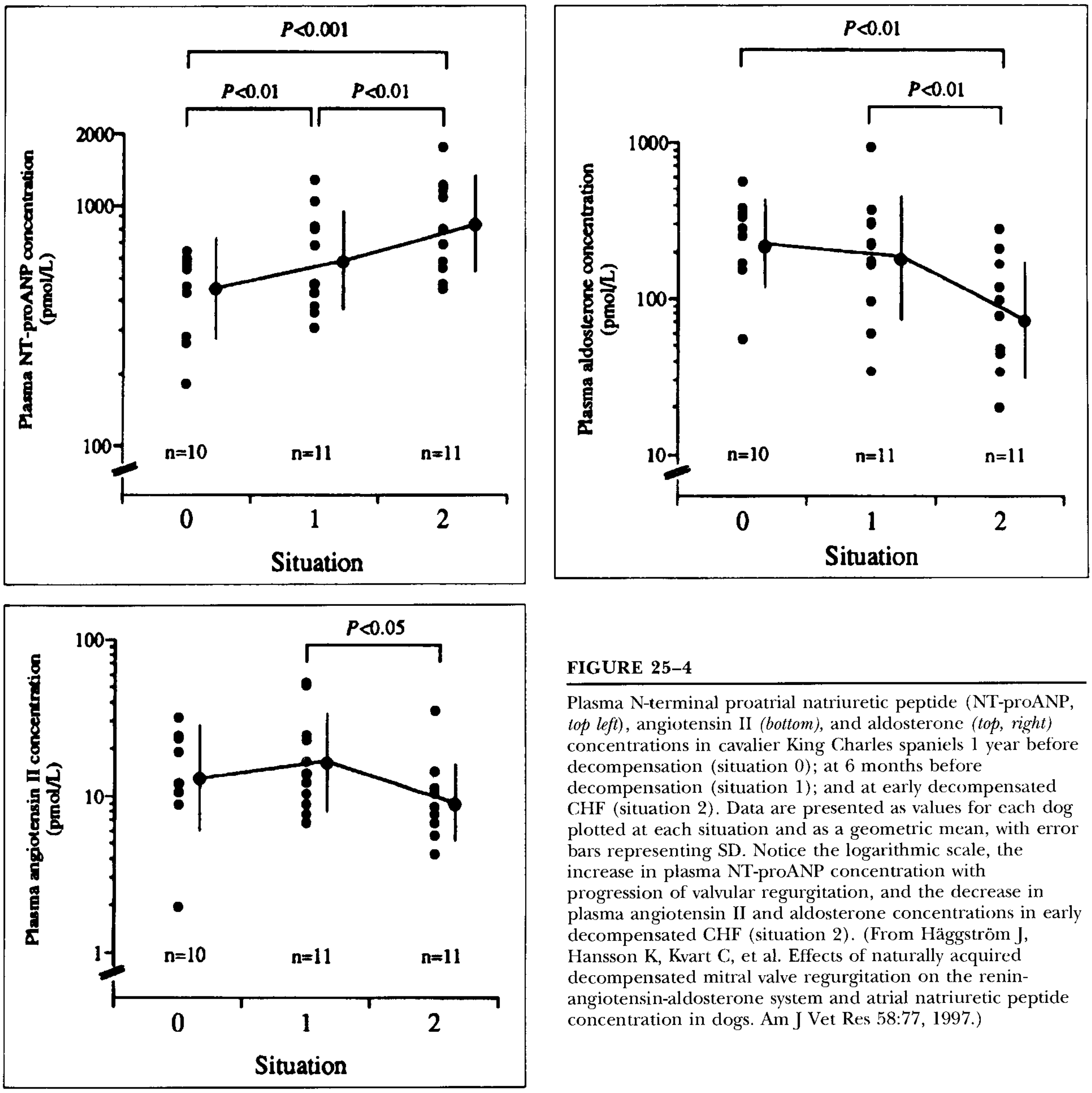


FIGURE 25-4

Plasma N-terminal proatrial natriuretic peptide (NT-proANP, *top left*), angiotensin II *(bottom)*, and aldosterone *(top, right)* concentrations in cavalier King Charles spaniels 1 year before decompensation (situation 0); at 6 months before decompensation (situation 1); and at early decompensated CHF (situation 2). Data are presented as values for each dog plotted at each situation and as a geometric mean, with error bars representing SD. Notice the logarithmic scale, the increase in plasma NT-proANP concentration with progression of valvular regurgitation, and the decrease in plasma angiotensin II and aldosterone concentrations in early decompensated CHF (situation 2). (From Häggström J, Hansson K, Kvart C, et al. Effects of naturally acquired decompensated mitral valve regurgitation on the renin-angiotensin-aldosterone system and atrial natriuretic peptide concentration in dogs. Am J Vet Res 58:77, 1997.)

in patients with mitral regurgitation only by methods that take into account cardiac loading conditions. This can be accomplished by determination of the mass-corrected end-ejection wall stress-volume relationship (EESVR), but this procedure is very cumbersome.[112, 113] The end-systolic wall stress/end-systolic volume ratio and end-systolic volume index are less accurate estimates of left ventricular function than EESVR, but they appear to be more useful indicators of contractility than the isovolumetric or ejection phase indices.[100–104] It is important to recognize that increased sympathetic nervous system activity can obscure the intrinsic decline in myocardial contractility occurring in dogs with mitral regurgitation. Acute β-adrenergic receptor blockade in dogs with chronic mitral regurgitation reveals a substantial reduction of the mass-corrected slope of the end-ejection stress-volume relation (EESVR). This unmasks the intrinsic depression of myocardial contractility not readily apparent prior to β-adrenergic blockade.[113] Thus, the severity of intrinsic myocardial impairment in dogs with naturally occurring mitral regurgitation has probably been underestimated.[5, 105]

The severity of clinical signs in dogs with CDVD and mitral regurgitation is not necessarily a reflection of myocardial function. Although progressive myocardial failure clearly contributes to the eventual clinical deterioration, severe pulmonary congestion may develop as a consequence of mechanical regurgitation of blood into the left atrium in the absence of myocardial failure (e.g., with traumatic rupture of a papillary muscle or sudden rupture of a chordae tendineae).[114, 115]

HISTORY AND CLINICAL SIGNS

Most clinical signs of mitral regurgitation result from pulmonary congestion (chapters 4, 5). Therefore, most dogs are presented for respiratory distress. Coughing is a common but nonspecific sign of developing heart failure in dogs, but not cats. Many older, small breed dogs cough because of chronic bronchitis or from a collapsing trachea. When coughing results from heart failure, there is usually an elevated respiratory rate (*tachypnea*) and increased respiratory effort (*dyspnea*). However, cough without dyspnea often occurs with severe mitral regurgitation and is thought to result from compression of the left main stem bronchus by an enlarged left atrium. Some dogs with CHF become restless at night, are unable to sleep, and experience *orthopnea* (i.e., have more difficulty breathing lying down than sitting or standing). Paroxysmal nocturnal dyspnea refers to severe attacks of orthopnea that occur several hours after the onset of sleep. When accompanied by audible wheezing, these episodes have been referred to as *cardiac asthma.*

Right-sided heart failure occurs in some dogs with CDVD due to myxomatous degeneration of the tricuspid valve (and resultant volume overload), as a consequence of pulmonary hypertension, or a combination of these disorders. Severe pulmonary hypertension occurs in a small minority of patients with chronic mitral regurgitation. Most of these dogs have serious underlying pulmonary disease. Rarely, signs of right-sided heart failure result from cardiac tamponade caused by a left atrial tear.[5, 116] The development of ascites is usually accompanied by signs of low-output heart failure and a decline in the severity of pulmonary congestion, regardless of etiology.

Generalized muscle weakness and progressive exercise intolerance become evident when forward output is impaired. This may result from severe valvular regurgitation, pulmonary hypertension, and/or declining myocardial contractility. Syncope tends to occur primarily when cardiac output declines precipitously. It is an uncommon sign in dogs with CDVD and is usually associated with a serious cardiac arrhythmia or paroxysms of coughing. Other causes are described in chapter 22.

Various schemes have been proposed to classify dogs with CDVD into disease stages. These are largely based on the attendant severity of clinical signs and/or radiographic findings.[115–119] The most familiar scheme for humans with heart failure was developed by the New York Heart Association (NYHA classes I–IV). A modification of this scheme is often used to classify dogs with heart disease (chapter 12).[120] Unfortunately, its clinical utility is limited by the paroxysmal nature of clinical signs in dogs, and the difficulties in detecting and quantifying subtle exercise limitations.

PHYSICAL EXAMINATION

Cardiac auscultation by a skilled examiner is the most practical and economic diagnostic method for detecting mitral regurgitation (chapter 5). The classic murmur of mitral regurgitation is holosystolic, constant in intensity, of mixed frequency, and loudest at the left apex (see Figs. 5–10, 5–11, 5–12).[115, 119, 121, 122] A soft, grade 1 of 6, systolic murmur over the mitral area (see Fig. 5–7) is the first clinical finding for CDVD. In some mildly affected dogs, the murmur occurs only intermittently at the end of inspiration. A mid or late systolic click or a click-murmur can sometimes be auscultated prior to the development of a holosystolic murmur. Presumably, the mechanism of the click-murmur in dogs is similar to what occurs in human patients with mitral valve prolapse.[27, 28 116, 123]

In cavalier King Charles spaniels, there is a strong relationship between murmur intensity, heart size, severity of regurgitation, and NYHA class of heart failure (Fig. 25–5).[73, 123] Cavaliers with a murmur of grade 3/6 or less and a clearly audible second heart sound are likely to have mild disease (NYHA class I or II, Fig. 25–6).[123] With disease progression, the murmur becomes louder, the second heart sound becomes softer or inaudible, and a gallop heart sound may be

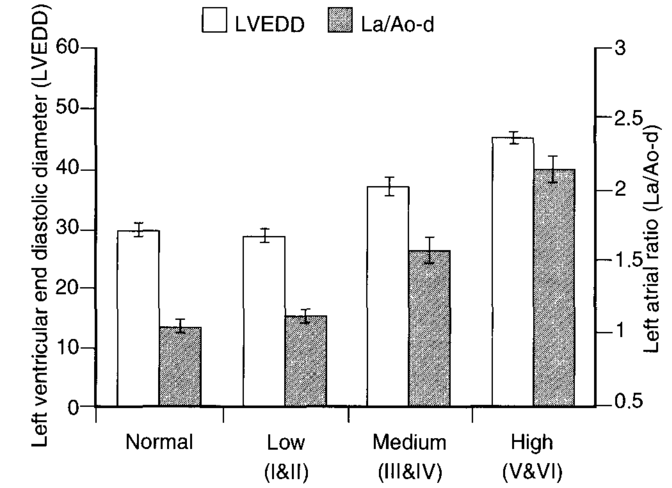


FIGURE 25–5

Mean left ventricular end-diastolic diameter (LVEDD) and left atrial ratio (La/Ao-d) echo measurements in 79 cavalier King Charles spaniels divided in 4 groups according to auscultated intensity of the heart murmur (grades 0–6) over the mitral area. Dogs with moderate-intensity (grades 3 and 4) and high-intensity (grades 5 and 6) murmurs differed significantly from both normal dogs and dogs with low-intensity murmurs ($p<.001$). The La/Ao-d and LVEDD were significantly ($p<0.001$) greater in dogs with high intensity murmurs (grades 5 and 6) than in dogs with moderate intensity murmurs (grades 3 and 4). Error bars represent ± SEM. (From Häggström J, Kvart C, Hansson K. Heart sounds and murmurs: changes relate to severity of chronic valvular disease (CVD) in the cavalier King Charles spaniel. J Vet Intern Med 9:75, 1995.)

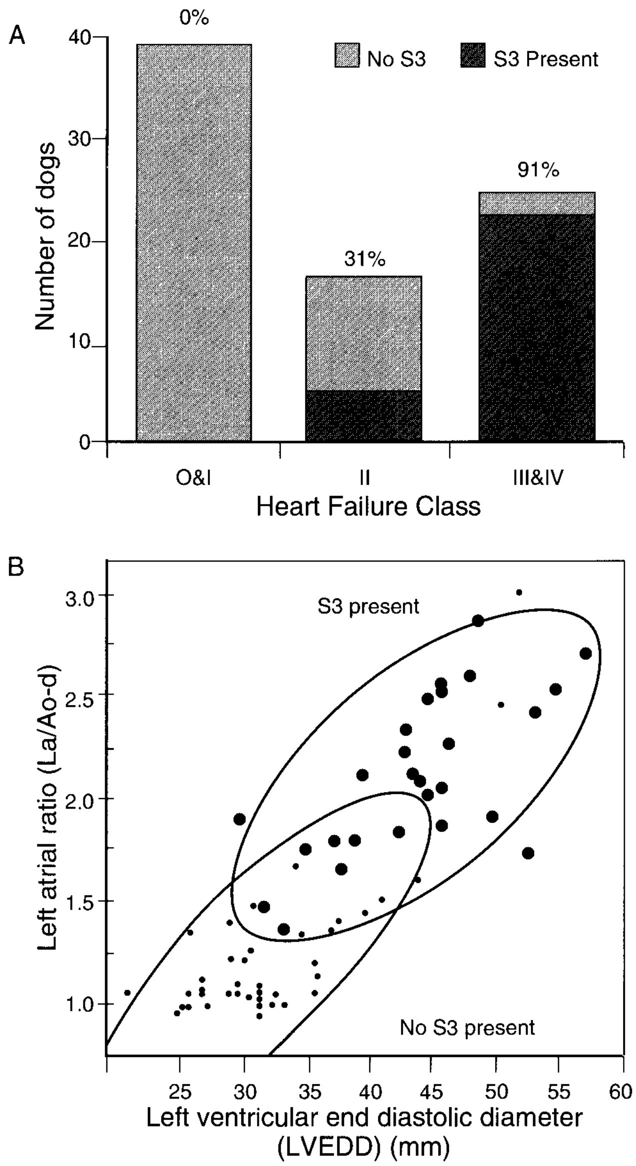


FIGURE 25–6

(A) Distribution of cavalier King Charles spaniels with S3 detected by phonocardiography in each heart failure class. (B) An S_3 was found among dogs with echocardiographic evidence of cardiomegaly (increased LVEDD and La/Ao-d). Small points represent dogs with no S_3, and large points represent dogs with S_3 present. The ellipsoids represent where confidence curves within each 90% of the data for each group (dogs exhibiting S_3 and dogs without S_3) are expected to be located. (From Häggström J, Kvart C, Hansson K. Heart sounds and murmurs: changes relate to severity of chronic valvular disease (CVD) in the cavalier King Charles spaniel. J Vet Intern Med 9:75, 1995.)

auscultated (see Fig. 5–10).[73, 123] An S_3 heart sound is often mistaken for the second heart sound when S_2 is obscured by the holosystolic murmur.[116, 123] With experience, gallop sounds can be readily identified as they are lower pitched than S_2 sounds and heard loudest at the cardiac apex.

Murmur intensity is a less reliable indicator of disease severity when a variety of breeds with differing conformations are examined. Occasionally, a loud, high-pitched, musical murmur, best described as a whoop or "sea gull-type" sound, is auscultated in a dog with mild to moderate valvular insufficiency. In such cases, systolic high-frequency vibrations of one of the mitral valve leaflets can often be documented by echocardiography.[124] Murmur intensity often varies with changes in contractility or loading conditions. Mitral regurgitation murmurs tend to become louder with exercise or excitement, and they may become soft or disappear when severe heart failure develops.[116]

The murmur of mitral regurgitation is usually best heard at the left 5th intercostal space (see Fig. 5–7), but dorsal, cranial, caudal, or rightward radiation of the murmur is common. It is particularly difficult to determine whether murmurs heard over the tricuspid valve area originate from that valve or whether they are referred from an incompetent mitral valve.[4, 5, 116, 121] Clinical evidence of tricuspid regurgitation, such as jugular pulsations, or radiographic or echocardiographic evidence of tricuspid insufficiency is often required to establish the diagnosis. Cardiac arrhythmias usually interrupt the predominating cadence of the heart, create abnormal pauses in the rhythm, and alter the intensity of both murmurs and transient heart sounds.

ELECTROCARDIOGRAPHY

Electrocardiograms are frequently normal in dogs with mitral regurgitation, even when cardiomegaly can be demonstrated on radiographs or an echocardiogram.[125–127] They may be more valuable when sequential recordings are performed.[116] At other times, P-wave prolongation (p-mitrale, >0.04 sec in dogs, >0.03 sec in cats) may be present due to left atrial enlargement (see Figs. 6–14*B*, 6–36). Left ventricular enlargement is suggested by prolongation of the QRS complex (>0.04 sec in cats, >0.06 sec in dogs) or by increased R-wave amplitude in leads II, III, and AVF (wave >0.9 mV in cats, >3.0 mV in dogs) (see Figs. 6–16, 6–39). The mean electrical axis is usually normal. Nonspecific ST segment and T-wave changes, reflecting the presence of hypertrophy, hypoxia, drug, and electrolyte alterations, may be observed.

Sinus rhythm (cats), sinus arrhythmia (dogs), or sinus tachycardia predominates in animals with mitral regurgitation. Heart rate and heart rate variability are not altered in dogs with slight to moderate left atrial and ventricular dilatation. However, heart rate is increased and heart rate variability is reduced once clinical signs of congestive heart failure are observed.[128] Premature ventricular and supraventricular beats are the most common rhythm disturbances recorded in dogs with mitral regurgitation.[4, 129] Atrial fibrillation develops in a small but substantial number of dogs with severe CDVD and is observed most often in male dogs with severe regurgitation and marked left atrial

enlargement.[4, 5, 116, 129] The onset of atrial fibrillation is usually accompanied by marked clinical deterioration.[4, 116] Paroxysmal or sustained supraventricular tachycardia, ventricular tachycardia, and other arrhythmias occur less frequently.

RADIOGRAPHY

Left atrial enlargement is the earliest and most consistent radiographic feature of mitral regurgitation (chapter 7).[116–119, 125] In the dorsoventral projection, the enlarged left auricle is initially recognized as a slight bulge protruding from the left cranial border of the heart, from the 2 to 3 o'clock position, using the clock face analogy (see Figs. 7–1*C*, 7–4*B*; and 25–7). Additional left atrial enlargement is usually accompanied by radiographic evidence of left ventricular enlargement. The entire left border of the heart becomes more convex, and the left atrial bulge may be obscured from view as the left ventricle enlarges. The enlarged cardiac silhouette eventually occupies a greater proportion of the thorax. The posterior border of the heart becomes rounded and may be displaced to either the left or right of the midline. It is not possible to distinguish pure left ventricular enlargement from biventricular enlargement on routine thoracic radiographs. As the left atrium dilates further, the main stem bronchi assume a more obtuse angle, and the body of the atrium may become visible as a dense mass superimposed on the caudal portion of the cardiac silhouette (see Figs. 7–4; 25–7).

In the lateral projection, left atrial enlargement causes the trachea to be displaced dorsally, diminishing the angle between the trachea and thoracic spine. The ventral deflection of the terminal trachea disappears. The left main stem bronchus is elevated by the enlarging left atrium and becomes visible dorsal to its counterpart on the right. Enlargement of the left atrium and ventricle causes the caudal border of the heart to flatten and then become more convex than normal. The dorsoventral and craniocaudal dimensions of the heart increase. Again, it is not possible to distinguish how much the left and right ventricles contribute to the obviously enlarged cardiac silhouette. Increased sternal contact may be evident in dogs with enlargement of either or both ventricles. Further dilatation of the left atrium, combined with dilatation of the proximal portions of the pulmonary veins, results in the formation of a wedge-shaped density that extends into the diaphragmatic lung fields (see Figs. 7–1, 7–4, 7–20; 25–7).

Thoracic radiographs are the most sensitive clinical indicator of pulmonary hemodynamics.[116, 118] As left-sided CHF develops, good-quality radiographs permit visualization of early changes in the pulmonary veins-lung interstitium. As pulmonary venous pressures rise, the pulmonary veins distend and become more evident centrally and in the peripheral lung fields. The dilated veins become denser and larger than the pulmonary arteries that accompany them (see Fig. 7–18). At this stage, there is an increased rate of transfer of fluid from the pulmonary capillaries to the interstitium (see Fig. 13–1). This is initially unapparent radiographically because the increased rate of interstitial fluid production is balanced by an increased rate of removal by pulmonary lymphatics (chapter 13). Further elevations of venous pressure result in radiographically detectable interstitial edema. Fluid accumulation in perivascular lymphatics and the interstitium causes the margins of pulmonary vessels to lose their crisp definition. Fluid accumulates in a similar fashion in the walls of the bronchi and bronchioles, causing peribronchiolar cuffing. The overall increase in pulmonary fluid content results in decreased radiolucency of the lung and a loss of contrast between the parenchyma and bronchovascular structures. These changes are often most apparent in hilar lung regions or in the right caudal lung lobes. In dogs, alveolar pulmonary edema, characterized by the appearance of indistinct fluffy densities, air alveolograms, and air bronchograms, develops initially in the hilar region or in the right caudal lung lobe (see Fig. 13–3). The location of such changes is more variable in cats.

CARDIAC CATHETERIZATION

Cardiac catheterization and angiocardiography are used mainly in a research setting to provide qualitative and semiquantitative estimates of the severity of regurgitation (see Figs. 9–10, 9–11).[89, 130–133] Mitral regurgitation can also be scored +1 to +4, based on the extent and duration of left atrial and pulmonary venous opacification following the injection of contrast material into the left ventricle.[130] Mitral regurgitant volume is more accurately estimated by measuring the difference between the angiocardiographically determined stroke volume and forward stroke volume as determined by Fick's method or by thermodilution.[89, 132] Measurement of pulmonary artery capillary wedge pressure (PCWP), via a balloon-tipped end-hole catheter (Swan-Ganz), is sometimes needed to clarify the nature of atypical pulmonary infiltrates in patients with mitral regurgitation. Pulmonary edema typically develops when mean PCWP approaches or exceeds 25 mmHg. A large v wave and exaggerated y descent are observed in the left atrial pressure tracing when marked mitral regurgitation is present (see Figs. 5–4; 9–7).

ECHOCARDIOGRAPHY

DETECTION OF REGURGITANT FLOW. Mitral regurgitation produces a high-velocity, turbulent jet of disturbed blood flow in the left atrium that can usually be de-

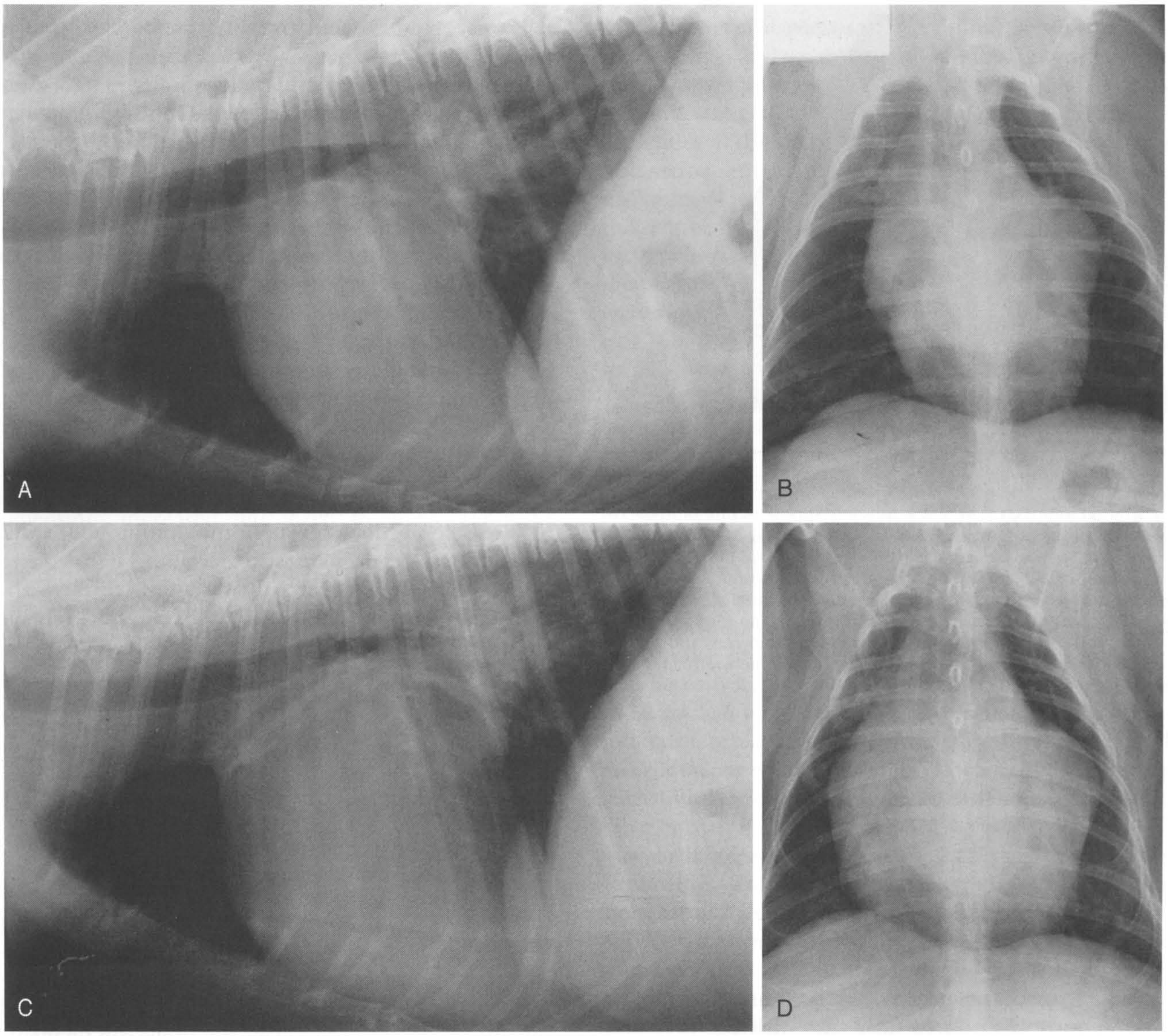


FIGURE 25–7

Thoracic radiographs illustrate progressive cardiac enlargement resulting from volume overload (mitral and tricuspid regurgitation) in an aged dog with chronic degenerative valvular disease. (A,B) At initial presentation, the dog was asymptomatic, but left atrial enlargement is pronounced. Three months later, the dog presented with signs of congestive heart failure due to pulmonary edema. (C,D) Six months after initial presentation, the dog had developed pulmonary hypertension and tricuspid regurgitation. Radiographs show marked enlargement of the left and right hearts relative to initial films (A,B).

tected by pulsed, continuous wave, or color flow Doppler echocardiography (see Figs. 8–5, 8–18; 25–8).[134] In most cases, severe mitral regurgitant flow continues throughout systole at a velocity of 5 to 6 meters per second. Flow velocity is a function of the pressure difference between the left ventricle and left atrium. In some cases, e.g., those with mitral valve prolapse, regurgitant flow may not be observed until mid to late systole. Regurgitant flow is virtually always turbulent flow, and it produces a broad spectrum of frequencies in the jet's Doppler velocity profile. Depending on the color flow display format of the echocardiograph, mitral regurgitant flow appears as a mosaic of yellow and blue pixels or as a bright green spray of color.

Color flow Doppler imaging allows a more thorough and much quicker means of inspecting the atria to find a regurgitant jet than does spectral Doppler echo (Fig. 25–8).[134] The sensitivity and specificity of Doppler techniques for the detection of mitral regurgitation are over 90 percent.[135] Small regurgitant jets in the immediate vicinity of the mitral valve should not be overinterpreted, however. Trivial mitral regurgitation can often be detected in normal dogs.[136, 137] Identification of concurrent tricuspid and/or aortic insuffi-

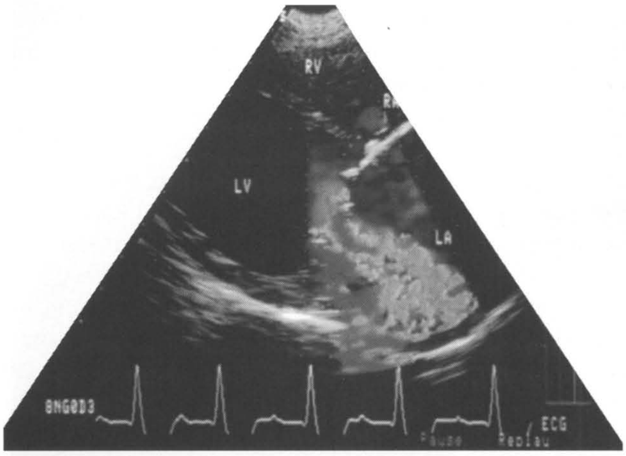


FIGURE 25–8

Gray scale reproduction of color flow Doppler echocardiogram from a dog with advanced mitral insufficiency. In the right parasternal long axis view, color flow jets appear as mottled pale areas within the atria during systole. The diameter of the regurgitant jet is quite large as it emerges from the mitral regurgitant orifice, indicating a large regurgitant volume. The length and area of the jet are less reliable indicators of regurgitant volume in this dog because the jet impinges on (and is constrained by) the posterior left atrial wall. There is left atrial *(LA)* and left ventricular *(LV)* dilation associated with the volume overload imposed by mitral regurgitation.

ciency can also be quickly and readily accomplished during the color flow examination.

COLOR FLOW JET SIZE. Jet size is proportional to momentum flux rather than to volume flow, and mitral regurgitant volume cannot be accurately determined from either length or area measurements of the regurgitant jet as displayed on the color flow Doppler echocardiogram.[134] Momentum flux is a function of the regurgitant orifice area and the driving pressure, which are related to volume flow by the Gorlin equation. Other problems confound the use of jet size to estimate regurgitant volume. Any true measure of regurgitant volume must integrate regurgitant flow rates over all of systole, and a color flow jet is an instantaneous measurement that reflects flow at a single time point. The direction, conformation, and size of a regurgitant jet often change during the systolic interval. Jet size is also influenced by a number of poorly controlled variables, including imaging plane, transducer location, the effective turbulent velocity of blood, left atrial size, proximity of the jet to the wall of the atrium, and many instrument settings such as gain settings, the pulse repetition frequency, and transducer frequency. In addition, jets that are constrained by the walls of the atrium are usually much smaller than free jets.

Despite these limitations, maximal jet area, indexed to left atrial size, correlates reasonable well with angiocardiographic measures of mitral regurgitant severity, particularly when eccentric jets impinging on the atrial wall are excluded from the analysis.[134, 138] In human patients, jet areas less than 20 percent of left atrial area correspond to mild mitral regurgitation; jet areas between 20 and 40 percent correspond to moderate regurgitation; and jet areas greater than 40 percent usually indicate severe mitral regurgitation.[139] The severity of regurgitation will be underestimated if gain is not optimized and whenever the jet is constrained by the left atrial wall. By comparison, jet length correlates rather poorly with regurgitant volume. In dogs, jet size shows a significant correlation with clinical scores of heart failure severity.[140] Other qualitative, semiquantitative, and quantitative methods have been developed for assessing the volume of mitral regurgitant flow.

FLOW VOLUME MEASUREMENTS. Mitral regurgitant stroke volume and regurgitant fraction can be estimated by echocardiographic methods that estimate forward blood flow through the mitral and aortic valves. Mitral regurgitant stroke volume is calculated as the difference between forward flow through the mitral valve during diastole and systolic flow out the aorta.[141–143] Forward flow is measured by integrating the Doppler velocity over the period of antegrade flow and multiplying that quantity by the annular cross-sectional area of each valve. Alternatively, mitral regurgitant flow can be calculated by subtracting aortic stroke volume, calculated as above, from the total LV stroke volume, which is calculated from M-mode or two-dimensional echocardiographic estimates of total left ventricular stroke volume.

PROXIMAL FLOW CONVERGENCE. Mitral regurgitant stroke volume can also be quantified using the proximal flow convergence method.[144–147] As flow approaches a pointlike orifice in a flat plate, a series of concentric hemispheric isovelocity shells can be identified with decreasing surface area and increasing velocity. Instantaneous flow rate can be calculated as the product of the velocity at any of these hemispheric shells times the area of the shell. Assuming simple hemispheric symmetry of the converging flow field, the proximal isovelocity surface area is calculated as $2\pi r^2$, where r is the radius measured from the first color alias to the regurgitant orifice. The peak instantaneous flow rate (ml/sec) is given by $Q\pi = 2\pi r^2 v_a$, where v_a is the aliasing velocity of the system. Mitral regurgitant stroke volume (V_r) is calculated by multiplying the peak instantaneous regurgitant flow rate by the regurgitant time-velocity integral ($\int v(t)dt$) normalized by the peak regurgitant velocity (v_p). Regurgitant flow, Q_r, is calculated by multiplying regurgitant stroke volume by heart rate:

$$Q_r = V_r \times HR = 2\pi r^2 v_a \int [v(t)/v_p]dt \times HR)$$

PROXIMAL JET DIMENSIONS. The diameter and cross-sectional area of the regurgitant jet as it emerges from

the regurgitant orifice have been shown to correlate well with angiographic grades and angiographic estimates of regurgitant volume in human patients, and to regurgitant flow measures obtained using the proximal flow convergence method.[148, 149] The proximal jet method is well suited to the routine evaluation of clinical patients as the jet dimensions can be obtained quickly and reliably from either transesophageal or transthoracic locations. This method has not yet been critically evaluated in dogs.

M-MODE AND TWO-DIMENSIONAL ECHOCARDIOGRAPHY. Most abnormalities detected by M-mode and two-dimensional echocardiography reflect changes caused by volume overload of the left-sided heart and are not specific for mitral regurgitation (see Figs. 8–22; 25–8, 25–9). These changes include an enlarged left atrial dimension, increased left atrial to aortic ratio, increased ventricular diastolic dimension, exaggerated septal motion and left ventricular wall motion, excessive mitral valve amplitudes of motion, and a steep E to F slope.[5, 105, 119, 125, 134, 150, 151] The identification of mitral regurgitation by finding a separation between the mitral leaflets during systole is unreliable. Structural abnormalities of the degenerative mitral valve identifiable by two-dimensional echocardiography include thickened valve leaflets, mitral valve prolapse (inclusive of tip protrusion into the left atrium), and flail leaflets caused by chordal rupture.[65, 114, 124, 134, 152–154]

MITRAL VALVE PROLAPSE. Mitral valve prolapse is defined as dorsal displacement of the mitral leaflets relative to the mitral annulus, as this structure defines the boundary between the left ventricle and left atrium.

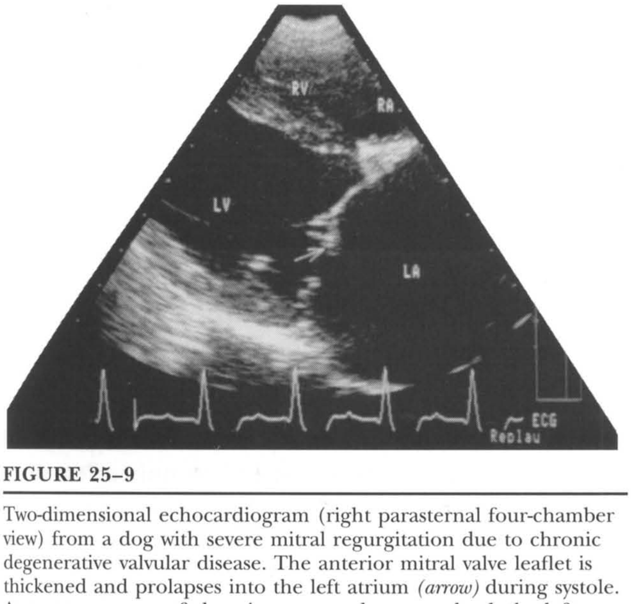


FIGURE 25–9

Two-dimensional echocardiogram (right parasternal four-chamber view) from a dog with severe mitral regurgitation due to chronic degenerative valvular disease. The anterior mitral valve leaflet is thickened and prolapses into the left atrium *(arrow)* during systole. As a consequence of chronic, severe volume overload, the left ventricle *(LV)* and especially, the left atrium *(LA)*, are dilated.

Mitral valve prolapse can precede but is often accompanied by varying degrees of mitral regurgitation. Mitral valve prolapse can best be identified by two-dimensional echocardiography (Fig. 25–9). Four characteristics of the valve have proved useful in identifying human patients with clinically important mitral valve prolapse: (1) the location of leaflet displacement, (2) the degree of leaflet displacement, (3) the presence of leaflet thickening, and (4) the symmetry of displacement.[134] In humans, mitral valve prolapse usually involves both leaflets, sometimes involves only the posterior leaflet, and only rarely involves only the anterior leaflet. However, the same may not be true in dogs. The views typically used to identify mitral valve prolapse include the right parasternal long axis view and the left caudal parasternal four-chamber view. Mitral valve prolapse is observed most often when the leaflets are thickened and redundant or when there is a loss of chordal support (stretching or rupture).

Using the right parasternal long axis view, Pedersen and associates reported that 84 percent of cavaliers with murmurs and 87 percent without murmurs had mitral valve prolapse, compared with a prevalence rate of 3 percent in age-matched control dogs.[153] In a study of 30 dachshunds with mitral regurgitation, severe mitral valve prolapse was identified in 40 percent, and mild prolapse was identified in 33 percent.[154] In young dachshunds without murmurs, none had severe mitral valve prolapse, but 7 of 15 (47 percent) had mild mitral valve prolapse. Further studies are needed to determine whether young dogs with mitral valve prolapse are at increased risk for mitral regurgitation compared with those dogs lacking this echo finding.

FLAIL LEAFLETS. Rupture of a major chordae tendineae (see Fig. 25–1) should be suspected when systolic fluttering of a prolapsed mitral valve leaflet is observed together with chaotic diastolic motion of a mitral valve leaflet.[65, 155–158] Ruptured chordae tendineae can be visualized only rarely. More often, rupture of a chordae tendineae must be inferred from the abnormal motion of the valve leaflets.[150] The flail motion of the valve cusps is usually best observed by two-dimensional echo imaging in the right parasternal long axis or by left apical four-chamber views.[65, 155–158] It may not be possible to distinguish stretching from rupture of a chordae tendineae, especially when a minor chordae is affected; both lesions cause varying mitral valve prolapse and regurgitation.

VENTRICULAR PERFORMANCE. Echocardiographic estimates of left ventricular contractility should be interpreted cautiously in dogs with mitral regurgitation, particularly the *ejection phase indices* (e.g., left ventricular fractional shortening, ejection fraction, and mean velocity of circumferential shortening), which are inaccurate in this setting.[77, 101–104, 159, 160] The values obtained

from dogs with mitral regurgitation are often normal or greater than normal owing to the ability of the left ventricle to decompress rapidly into the low-pressure left atrium. Therefore, in the setting of moderate to severe mitral regurgitation, a normal ejection fraction represents a significant reduction of myocardial contractility.[101–104, 159–160] *End-systolic volume indices* more accurately estimate myocardial contractility in dogs with mitral regurgitation.[159–161] However, when heart failure is present and the sympathetic nervous system is activated, even these measurements overestimate intrinsic myocardial contractility.[107, 108]

DIFFERENTIAL DIAGNOSIS

The diagnosis of mitral regurgitation due to chronic degenerative valvular disease is usually made from the clinical history, the physical examination, and good quality thoracic radiographs. Coexisting abnormalities, such as chronic bronchitis, a collapsing trachea, or pneumonia, can be easily overlooked unless current thoracic radiographs are evaluated in conjunction with the physical examination. Therefore, a dog with a heart murmur that is presented for coughing or dyspnea should be carefully evaluated for upper and lower respiratory disease. Collapse of the left main stem bronchus by an enlarged left atrium is a common cause of chronic coughing that is unrelated to the development of pulmonary congestion. When pulmonary infiltrates of uncertain origin are identified, several diagnostic options are available. If the infiltrates resolve following administration of diuretics, the likely etiology was pulmonary congestion due to left-sided heart failure. Should they fail to resolve, additional diagnostic procedures should be pursued, such as transtracheal or bronchoalveolar lavage, or fine needle aspiration.

Echocardiography should be performed when the location, cause, or importance of a murmur is uncertain and whenever other clinical tests yield apparently contradictory information. Loud murmurs of either atrioventricular valve may radiate widely, and it is often difficult to tell whether the mitral, the tricuspid, or both valves are incompetent. Color flow Doppler echocardiography resolves such issues quickly and reliably and is also well suited to differentiate other etiologies of mitral valve disease and mitral regurgitation. Echocardiography cannot, however, always reliably distinguish chronic degenerative valvular disease from bacterial endocarditis of the mitral valve. Recognition of the systemic manifestations of endocarditis and the performance of properly obtained blood cultures may be required to establish a diagnosis in such cases (chapter 26).

Careful assessment of other systemic disorders is often neglected in dogs with heart failure from CDVD. Given the high prevalence of renal disease and hyperadrenocorticism in old dogs, it is always prudent to complement the cardiac evaluation with a complete blood count, chemistry profile, and urinalysis. Blood pressure should be routinely determined in older dogs with mitral regurgitation inasmuch as systemic hypertension substantially worsens the severity of mitral regurgitation. Chronic anemia, concurrent infections, heartworm disease, and other serious disorders must also be identified to ensure optimal management.

THERAPY

Most of the schemes developed to stage dogs with mitral regurgitation are based on clinical signs and radiographic findings.[116–119] Echocardiography, while not generally essential for diagnosis and management, does provides more accurate assessment of heart size and allows visualization of valve morphology. Color flow Doppler echocardiography provides further estimation of regurgitant volume. This information, in combination with the history, physical examination, ECG, and chest radiographs, permits the most accurate assessment of disease severity and requirement for treatment.

Specific treatment goals are to reduce the severity of mitral regurgitation, to prevent or alleviate pulmonary congestion, to maintain cardiac output, to preserve remaining cardiovascular reserves, and to prevent or manage aggravating conditions or complications. The priority attached to any one of these goals varies with the specific requirements of the individual patient. Overall treatment objectives are to increase survival and improve quality of life.

SURGICAL ALTERNATIVES. The definitive remedy for mitral regurgitation in human patients is surgical repair or replacement of the damaged valve.[89, 162–164] Repair methods include ring and plication annuloplasty, resection of prolapsing valve segments, and shortening, reattachment, or replacement of ruptured chordae tendineae. Surgical repair of the mitral valve is more difficult to accomplish than valve replacement, but this approach has definite mechanical advantages and avoids the need for long-term anticoagulation.[89] Prior to the recent refinements in reparative surgical techniques, surgery was recommended only for severely impaired patients (NYHA class III or IV). Currently, surgery is often advised for patients with more modest physical impairment (NYHA class II).[89] For optimal results, surgery must be accomplished prior to the development of irreversible myocardial damage. Mitral valve surgery has been performed in only a few dogs with naturally occurring disease, due largely to the expense of cardiac bypass surgery.[165–167]

MEDICAL MANAGEMENT. The ideal medical treatment would prevent or reverse valvular degeneration by tar-

geting the precise molecular and biochemical defect(s) responsible for the myxomatous degenerative lesions. By manipulation of the enzymes regulating collagen metabolism, it may be possible in the future to modify the cascade of events causing distortion and disruption of the valve leaflets and chordae tendineae. Current therapy is designed to prevent congestion, to reduce the severity of mitral regurgitation, and to moderate the adverse consequences of chronic neurohormonal activation (chapter 12).

Diuretics, vasodilators, angiotensin-converting enzyme inhibitors, and positive inotropic drugs have the demonstrated capacity to lessen the severity of mitral regurgitation under certain conditions.[82–89] The relative merits of specific agents vary with the clinical circumstances of each patient. In general, patients with acute congestive heart failure respond best to diuretics and rapidly acting vasodilators. The current standard of therapy for dogs with chronic congestive heart failure due to mitral regurgitation is the "FAD" protocol: combination therapy using (f)urosemide, an (A)CE inhibitor, and (d)igoxin.[168, 169] Dogs requiring medical therapy should avoid strenuous exercise, and increasingly severe exercise restriction should be enforced as the disease progresses.

DIURETICS AND SALT RESTRICTION. Dietary salt restriction, diuretic therapy, or both are instituted at the first sign of CHF to eliminate excess body fluids and relieve pulmonary congestion. Improved myocardial oxygenation improves cardiac performance, and the severity of regurgitation may lessen as a result of the decreased preload and afterload that accompanies a reduction in heart size. Neurohormonal activation is an unavoidable consequence of diuretic treatment, but these responses can be minimized when diuretics are used in lower doses and/or in combination with ACE-inhibiting drugs.[170] Feeding a sodium-restricted diet may reduce the need for diuretics and may lessen the severity of neurohormonal activation.

Furosemide is the drug chosen most often for treating mitral regurgitation because it is effective and well tolerated by both dogs and cats. The lowest dose that controls clinical signs should be used. As heart failure progresses, higher and more frequent dosing is often required. When fulminant pulmonary edema is present, higher doses (2 to 4 mg/kg) should be given intravenously until the animal is stable (e.g., q 1 to 4 hr as needed in emergency settings). In refractory heart failure, furosemide can be combined with another diuretic with a different mechanism of action to achieve a synergistic effect (chapter 12).

Certain cautions should be observed with diuretic administration. Overzealous diuresis can decrease preload to the extent that cardiac output falls substantially. Overdiuresis in concert with ACE inhibitor administration can cause functional renal insufficiency. Diuretics should also be used cautiously when signs of low-output failure are present (e.g., weakness, prolonged mucous membrane perfusion and poor color, hypokinetic femoral arterial pulses, and tachycardia), or in states of ventricular underfilling (e.g., cardiac tamponade).

ACE INHIBITORS. The efficacy of ACE inhibitor therapy is well established in dogs with experimental[171, 172] and naturally occurring mitral regurgitation.[93, 173–179] In dogs with class III or class IV heart failure due to CDVD, chronic treatment with an ACE inhibitor in combination with furosemide and digoxin alleviates the signs of heart failure and improves exercise tolerance better than treatment with furosemide and digoxin alone. There are no published studies documenting the benefits of ACE inhibition in the early stages of heart failure (class I or II) in dogs with chronic degenerative valvular disease. Sodium and water retention in the early stages of heart failure may not be mediated by the R-A-A system, suggesting that drugs other than ACE inhibitors are required to normalize plasma volume in dogs with developing heart failure.

Adverse effects of ACE inhibitors include renal failure, hypotension, and hyperkalemia.[168, 169, 175] Renal dysfunction is the most common and most serious complication of ACE inhibitor therapy. Dehydration, hypotension, profound heart failure, pre-existing renal dysfunction, and treatment with high doses of diuretics increase the risk of serious renal dysfunction. Renal function should be carefully assessed prior to treatment with an ACE inhibitor, and BUN or serum creatinine levels should be periodically monitored during treatment. Other vasodilators can be used when ACE inhibitors are not tolerated (chapter 12).

DIGITALIS GLYCOSIDES. The use of digitalis glycosides in dogs with mitral regurgitation remains somewhat controversial.[5, 105, 168, 180] While persuasive evidence exists that myocardial contractility eventually declines in dogs with mitral regurgitation, it is very difficult to assess accurately the level of myocardial contractility and to identify the onset of myocardial failure. Many cardiologists initiate digoxin therapy together with diuretics and ACE inhibitors when the signs of CHF first appear. This strategy supposes that digoxin can reduce the severity of regurgitation prior to the onset of myocardial failure, retard the development of myocardial failure, and/or cause long-term symptomatic improvement.[106] Others institute digoxin only in the later stages of heart failure when diuretics, ACE inhibitors, or vasodilators are no longer able to control the clinical signs and when there is more dramatic myocardial impairment.[168, 169] There is no proven advantage to either strategy. Digoxin is always indicated when heart failure is complicated by atrial fibrillation and a fast heart rate. The negative chronotropic effect of digoxin

allows for improved ventricular filling and a larger stroke volume. Optimal control of heart rate may require the addition of a calcium channel (diltiazem) or β-adrenergic (atenolol, propranolol) blocking drug.

VASODILATORS. Other vasodilators are used when ACE-inhibiting drugs are not tolerated or when the signs of heart failure cannot otherwise be controlled (refractory heart failure). The short-term hemodynamic benefits of vasodilator therapy have been convincingly demonstrated in dogs with experimentally induced[87, 88] and naturally occurring[181–183] mitral regurgitation. Questions that remain unanswered concern the length of time hemodynamic benefits are maintained, the prevalence of adverse reactions, and the relative merits of particular arteriolar, venous, and mixed vasodilating agents.

Hydralazine is a direct-acting arteriolar vasodilator that has been shown effective in the short-term management of chronic mitral regurgitation in dogs.[181–184] Problems encountered with its use include a variable dose requirement, tolerance with long-term administration, and adverse side effects such as hypotension, tachycardia, anorexia, and other gastrointestinal signs.[168, 181–184] Drug titration (start at 0.5 mg/kg q 12 hr PO) is necessary to determine the appropriate dose (0.5 to 2 mg/kg q 12 hr). Hydralazine is generally used in combination with an oral or cutaneously applied nitrate to achieve balanced vasodilation.[185]

Amlodipine, a calcium channel blocking drug, has been proved to reduce symptoms and improve exercise tolerance in humans with congestive heart failure.[186] The efficacy of this compound in dogs with CDVD has not been determined, but preliminary observations suggest it is efficacious in dogs with heart failure complicated by systemic hypertension and in normotensive dogs with otherwise refractory heart failure. A safe and effective dose has not been established. When dogs with experimentally induced systemic hypertension are treated with amlodipine (0.05 to 0.2 mg/kg), blood pressure declines slowly, reaching a nadir in 6 to 8 hours after the first dose.[187] Tachycardia can occur when higher doses are used. The half-life in dogs is about 30 hours; thus, steady-state concentrations are not reached for 4 to 7 days.[188]

Nitroglycerin ointment, isosorbide dinitrate, and isosorbide mononitrate are direct-acting venous vasodilators. By increasing systemic venous capacitance, these drugs effectively lower pulmonary venous pressure, thereby relieving signs of pulmonary congestion. Hemodynamic benefits are sustained in most human patients receiving nitrate therapy, and side effects are relatively uncommon.[189] Lower LV filling pressures and reduced LV size may induce a decline in regurgitant volume. Although commonly used in dogs with CHF, topical nitroglycerin ointment has not been critically evaluated for safety or efficacy. Transdermal nitroglycerin cream should be applied on a hairless or shaved area, using gloves to avoid absorption by the person administering the medication. Self-adhesive transdermal nitroglycerin patches have been used in dogs and cats to ensure more uniform drug delivery. Patches delivering 0.1 mg/hr (in humans) have been recommended for treating cats and small dogs, and patches delivering 0.2 mg/hr were recommended for larger dogs.[168]

Isosorbide dinitrate is available in a sublingual formulation, a standard oral formulation, and as a controlled-release capsule and tablet. An empiric dose of the standard oral formulation (Isordil) used in dogs with heart failure is 0.22 to 0.44 mg/kg q 8 hr.[168] Isosorbide dinitrate has been dosed as high as 2.0 mg/kg q 12 hr in dogs with experimentally created myocardial infarcts.[190] Isosorbide mononitrate, the primary metabolite of isosorbide dinitrate, may also be useful in dogs with heart failure.[191, 192] From these studies, the estimated oral dose of isosorbide mononitrate in dogs is 0.25 to 2.0 mg/kg q 6 to 12 hr. In human patients, a dosage-free interval, typically 10 to 12 hours long, is advised to avoid the phenomenon of tolerance. The utility of this maneuver in dogs or cats with heart failure is unknown.

Prazosin is an α-adrenergic blocking agent causing arteriolar and venous vasodilation.[189] In human patients, the dosage is less variable than that of hydralazine, and adverse reactions are uncommon.[189] The main criticism of this agent concerns its effectiveness for long-term therapy.[189] Tachyphylaxis may develop within 48 to 72 hours in some human patients. Prazosin has not been critically evaluated in dogs with heart failure and has fallen into disfavor.

ANCILLARY THERAPIES. Oxygen therapy is always beneficial in hypoxemic patients with pulmonary edema. Morphine sulfate can be used to relieve anxiety and to lessen pulmonary congestion, particularly in nervous dogs. Some dogs, typically those with concurrent respiratory disease, appear to benefit from theophylline or aminophylline administration. Cough suppressants are avoided unless they are needed to control the signs of coexisting conditions, such as collapsing trachea. Antiarrhythmic drugs may be needed to eliminate life-threatening or hemodynamically unstable arrhythmias.

TREATMENT OF SEVERE OR REFRACTORY HEART FAILURE. Intravenous agents are generally reserved for dogs with severe acute heart failure or chronic heart failure that is nonresponsive to maximally tolerated oral doses of digoxin, diuretics, and ACE inhibitors. High-dose intravenous furosemide (e.g., 2 to 6 mg/kg) often resolves pulmonary congestion in animals with refractory heart failure. Dobutamine can also be used in combination with an intravenous vasodilator, such as nitro-

prusside, to stabilize patients with otherwise intractable heart failure. Both drugs are administered by constant intravenous infusion and are primarily used to treat chronic, refractory heart failure or acute, life-threatening pulmonary edema due to mitral regurgitation associated with ruptured chordae tendineae. Hypotension is the most hazardous side effect of nitroprusside but can be reversed within 10 minutes by simply discontinuing the drug. Most patients are weaned from IV onto oral therapy within 24 to 48 hours.

PROGNOSIS

It is difficult to predict the clinical course of CDVD in an individual patient. Many dogs with chronic valvular disease remain compensated throughout life and eventually die or are euthanized for reasons other than the development of heart failure.[115] Once signs of severe heart failure develop, the prognosis for long-term survival is often poor. In a long-term trial evaluating the efficacy of enalapril, the average survival time for dogs in NYHA class III or IV heart failure was less than 1 year for both treatment groups (Freedom of Information Summary #315). Many dogs with CDVD suffer repeated acute exacerbations of congestive heart failure that sporadically interrupt long or short periods of apparent remission. The rate of progression and eventual outcome of CDVD vary in different breeds. Rapid progression seems to be the rule in certain breeds, such as cavalier King Charles spaniels (Fig. 25–10).

The progression of CDVD has been prospectively studied in a group of 61 animals selected as representative of the cavalier King Charles spaniel population in Sweden.[193] Murmurs were initially found in 52 percent of all dogs. When this group of dogs was examined 3 years later, 28 percent of those dogs with murmurs 3 years earlier had died from heart failure. The average age at death or euthanasia was 10.6 years. All the dogs free from murmurs at the first examination were alive, but 48 percent had developed murmurs.[193] The mean time span between onset of murmur and euthanasia due to CDVD was approximately 3 to 4 years (Fig. 25–11). Despite the fact that heart murmurs are reported equally among male and female cavaliers, euthanasia due to heart failure is more common in males.[72, 193] This can be explained by an earlier onset of the disease in males and, perhaps, a faster progression of the disease.[194]

SYNDROMES ASSOCIATED WITH CHRONIC DEGENERATIVE VALVULAR DISEASE

RUPTURE OF THE CHORDAE TENDINEAE. Rupture of the chordae tendineae occurs in three different circumstances: (1) as an incidental finding at necropsy, (2) in dogs with a prior history of chronic mitral regurgitation, and (3) as a distinct clinical syndrome characterized by the sudden development of severe, fulminating pulmonary edema in previously asymptomatic dogs.[116, 195–197] Of 28 affected dogs studied by Ettinger and Buergelt, 17 were males, the age range was 7 to 17 years, and most dogs were poodles (10/28), cocker spaniels (4/28), beagles (4/28), and dachshunds (2/28).[196] These sex, age, and breed predilections are similar to those reported in dogs with chronic myxomatous valvular degeneration.[4, 116] Myxomatous degeneration of the atrioventricular valves is found in most dogs with ruptured chordae tendineae at necropsy, but there is little correlation between the severity of valvular lesions and rupture of the chordae tendineae.[126] This fact has prompted some investigators to consider alternative or additional etiologic factors.

The consequences of chordae tendineae rupture are

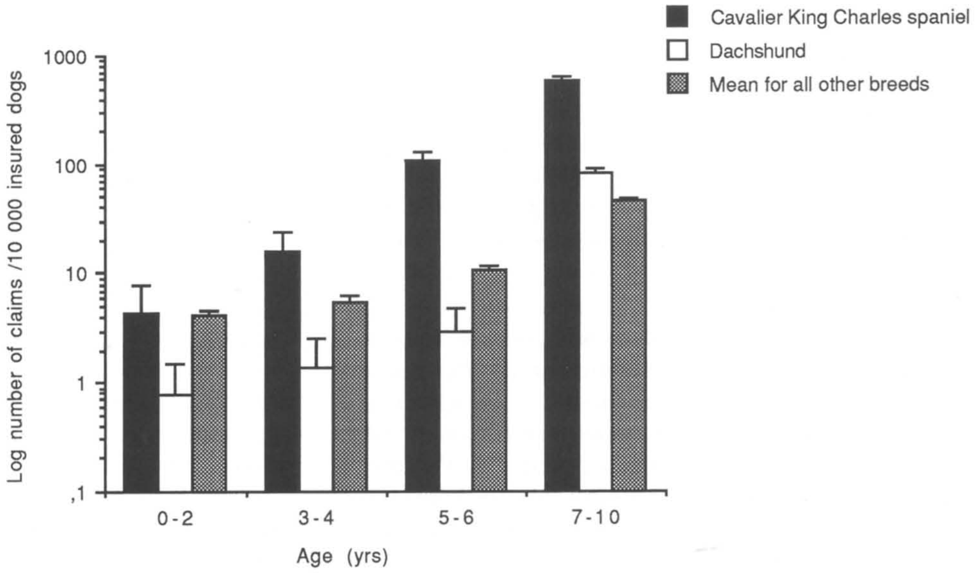


FIGURE 25–10

Mean annual number of claims per 10,000 insured dogs in Sweden for death/euthanasia caused by cardiac disease during 1982 to 1990 (1983 excluded). Data are presented in age groups on a logarithmic vertical axis. The overall frequency of claims per 10,000 insured dogs was five times higher in the cavalier than in the Dachshund, and eight times higher than the mean for all other breeds. Error bars show calculated 95% confidence limits. (From Häggström J, Hansson K, Kvart C, et al. Chronic valvular disease in the cavalier King Charles spaniel in Sweden. Vet Rec 131:549–553, 1992.)

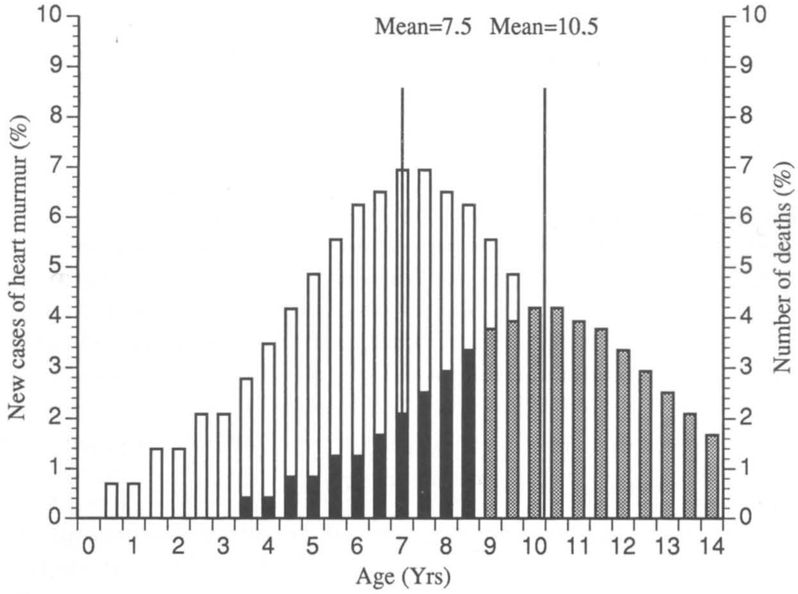


FIGURE 25–11

Proposed epidemiologic model of chronic degenerative valvular disease in the cavalier King Charles spaniel. The average time span from the onset of the heart murmur to death/euthanasia due to congestive heart failure is estimated to be 3 years. This graph illustrates the percentage of new cases of heart murmurs in each age group; the percentage of deaths due to congestive heart failure in each age group based on insurance statistics (Agria Ltd, Stockholm, Sweden); and the predicted percentage of deaths due to congestive heart failure, assuming the total percentage of deaths due to heart failure to be 40% of the population. (Courtesy of J. Häggström, DVM, College of Veterinary Medicine, Uppsala, Sweden.)

determined mainly by the location of the chordae torn (see Fig. 25–1).[198, 199] Clinical signs are most severe when one or more first-order chordae tendineae of the anterior (septal) leaflet of the mitral valve are torn. Less severe signs result from rupture of the first-order chordae tendineae of the posterior (mural) leaflet. Rupture of second- or third-order chordae may result in minimal or no clinical signs. Sudden deterioration in a dog with pre-existing mitral regurgitation suggests the possibility of chordae rupture. Rupture of tricuspid valve chordae tendineae can also occur and usually involves those of the septal leaflet.[4, 196]

Rupture of a first-order chordae tendineae often results in acute (often less than 12 hours), rapidly progressive signs; severe, intractable pulmonary edema;[116] and profound respiratory distress and cyanosis. A gallop rhythm and precordial thrill are accompanied by a loud, grade V to VI/VI, holosystolic, left apical murmur. The femoral artery pulse is typically abrupt or jerky, and a jugular venous pulse is often evident. A variety of rhythm disturbances may be observed, including ventricular arrhythmias and atrioventricular dissociation. The radiographic signs are similar to those seen in chronic mitral regurgitation with severe pulmonary edema. Atrial enlargement is variable and a function of the presence and severity of pre-existing mitral regurgitation.

THERAPY. Aggressive therapy is indicated in dogs with ruptured chordae tendoneae and fulminating pulmonary edema. Oxygen administration is usually required, coupled with a potent afterload reducer such as nitroprusside, and high-dose, frequent IV furosemide administration. Phlebotomy can be considered when these measures fail. The prognosis is often grave, and death commonly results.[116, 196]

LEFT ATRIAL ENDOCARDIAL TEARS AND LEFT ATRIAL RUPTURE. Left atrial rupture due to endocardial splitting of the left atrial wall is a well-characterized but uncommon complication of chronic, severe mitral valvular disease.[4, 5, 115, 200–205] This sequela occurs most often in older male dogs, and dachshunds and cocker spaniels are reported to be most commonly affected. In a series of 30 dogs[203] with left atrial tears, about half (17 of 30) were nonperforating, and about one third (9 of 30) had hemopericardium resulting from perforation of the left atrial epicardial surface; acquired atrial septal defect was demonstrated in four dogs following rupture of the interatrial septum. Endocardial splitting occurred most often in the caudal left atrial wall in association with pre-existing jet lesions. Severe, chronic mitral valvular lesions and massive left atrial enlargement were present in nearly all affected dogs, and ruptured first-order chordae tendineae were observed in many. Buchanan has hypothesized that a genetically influenced degeneration of connective tissue predisposes certain breeds to the development of left atrial tears, and that rupture of the chordae tendineae often precipitated this lesion by causing a sudden rise in interatrial pressure.[203]

Hemopericardium from left atrial rupture often results in sudden death from acute cardiac tamponade (Fig. 25–12). In other dogs with pre-existing mitral regurgitation, the sudden development of ascites, hepatomegaly, and jugular distention signals the occurrence of pericardial hemorrhage. Muffling of heart sounds may be detected, but more typically, this finding is obscured owing to the presence of a loud, holosystolic murmur. Femoral artery pulses are usually weak, and pulsus paradoxus may be evident. The ECG may be normal or reflect left-sided heart enlargement. The dampened, low-amplitude QRS complexes often

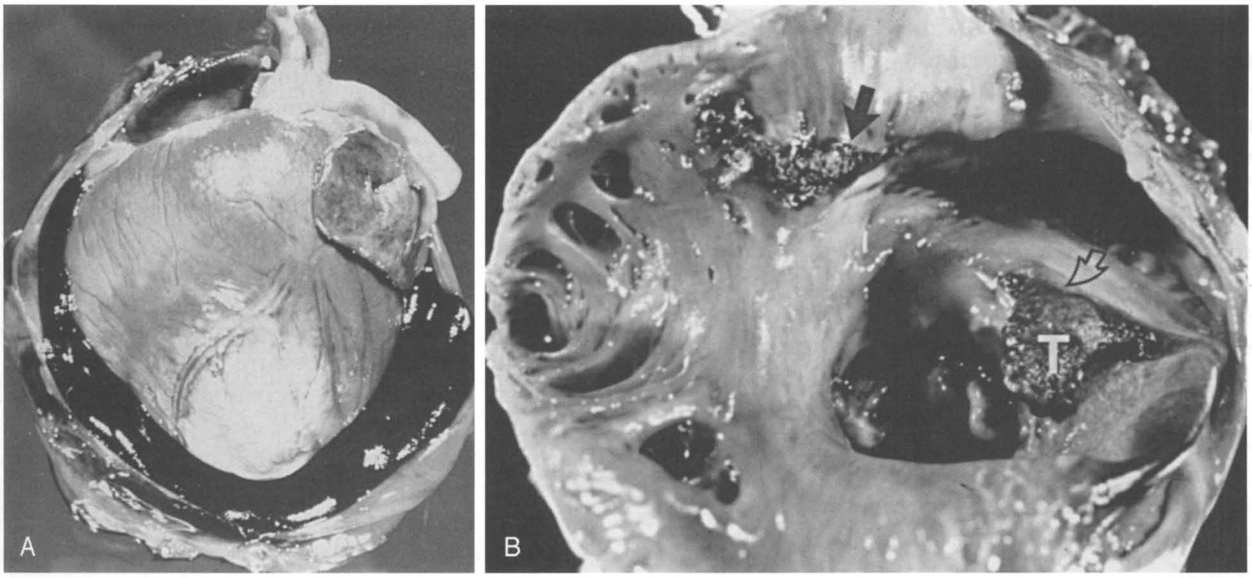


FIGURE 25–12

Cardiac tamponade and death are common in dogs experiencing left atrial rupture associated with chronic degenerative valvular disease (myxomatous degeneration). (A) The heart of a dog with chronic mitral regurgitation is surrounded by a large, intrapericardial blood clot within the opened pericardial sac. (B) Inspection of the left atrial endocardial surface reveals a recent tear *(solid arrow)*; an older tear *(open arrow)* is also present with an attached thrombus *(T)*. Grossly thickened and distorted mitral valve leaflets are visible lining the atrioventricular orifice, just left of the thrombus. Ruptured chordae tendineae were present. (From Sisson D. Acquired valvular heart disease. *In* Bonagura JD (ed): Contemporary Issues in Small Animal Practice. Cardiology. New York, Churchill Livingstone, 1987, p 59.)

observed with other causes of pericardial effusion are not usually evident unless a previously recorded ECG is available for comparison. Electrical alternans and a variety of rhythm disturbances may be recorded, particularly supraventricular extrasystoles, atrial and junctional tachycardias, and atrial fibrillation.

The diagnosis is often suggested by thoracic radiographs. In the dorsoventral projection, the silhouette is globular in appearance and is not dissimilar in any way from other causes of pericardial effusion. In the lateral projection, the cardiac silhouette may also appear rounded, but the enlarged left atrium is usually clearly evident as a triangular extension of the dorsocaudal heart border. Echocardiography is the most sensitive modality to detect pericardial effusion. Left atrial rupture is suggested when pericardial effusion is observed together with the typical echocardiographic features of chronic mitral regurgitation, particularly when blood clots are imaged within the pericardial sac.[5, 201–203]

An extremely uncommon sequela to chronic mitral regurgitation occurs when the atrial septum is ruptured, creating an acquired atrial septal defect.[201, 203] Severe right-sided heart failure and refractory ascites then develop in dogs that previously exhibited evidence of mitral regurgitation. Antemortem diagnosis can be accomplished with color flow Doppler echocardiography. The diagnosis of nonperforming endomyocardial splits cannot usually be made prior to necropsy except when an attached intra-atrial thrombus is imaged by echocardiography or angiocardiography.

THERAPY. Treatment of any dog with acute pericardial tamponade involves immediate pericardiocentesis. The possibility of continued hemorrhage exists, and this may necessitate blood transfusion or an emergency thoracotomy. Thoracotomy may be required to remove large clots in the pericardial sac that restrict cardiac filling, although surgical repair of the left atrium can occasionally be accomplished.[205] The prognosis is grave.

TRICUSPID REGURGITATION

Tricuspid valve insufficiency is conveniently classified into organic and functional types. Organic (primary) tricuspid regurgitation indicates that the valve leak is due to structural damage to the tricuspid valve apparatus, whereas functional tricuspid valve insufficiency develops secondary to enlargement (dilation) of the right side of the heart. Myxomatous degeneration of the valve leaflets or chordae tendineae is the only common cause of organic tricuspid regurgitation in dogs.[1–5] Kersten,[206] Bretschneider,[3] and Buchanan[4] reported involvement of both the mitral and tricuspid valves in 44.3 percent, 22.6 percent, and 32.5 percent of dogs with CDVD, respectively. Only 1.3 percent to

7.5 percent of the dogs with CDVD had isolated involvement of the tricuspid valve.[3, 4, 206] These findings have been corroborated.[1, 2, 31–37] Other causes of organic tricuspid regurgitation, such as bacterial endocarditis, are rare in dogs and cats.

Functional tricuspid regurgitation is often observed in dogs with dilated cardiomyopathy, and it is a common sequela to right-sided heart dilation caused by pulmonary hypertension from a variety of etiologies.[5, 152, 207] In cats, tricuspid regurgitation is observed most often in association with idiopathic myocardial disease and less frequently secondary to chronic hyperthyroidism.[207, 208] The overall prevalence of functional tricuspid regurgitation in dogs or cats with these disorders is unknown and undoubtedly varies with the severity of the underlying disease, the severity of pulmonary hypertension, and the degree of right-sided heart enlargement.

ANATOMY OF THE TRICUSPID VALVE

The adjective "tricuspid" is somewhat of a misnomer when applied to the dog's right atrioventricular valve, which consists mainly of two cusps.[17] A large mural (ventral or parietal) cusp and a smaller septal (or dorsal) cusp can be identified, together with several unnamed secondary cusps. The parietal cusp is essential for effective valve closure, whereas excision of the septal leaflet does not cause tricuspid regurgitation in otherwise healthy dogs in sinus rhythm.[209] The area of the tricuspid orifice (annulus) is slightly larger than that of the mitral orifice, and the tricuspid valve leaflets are thinner and more transparent than the mitral valve leaflets.[39] The chordae tendineae of the mural leaflet attach to a single, constant, small papillary muscle of the conus and to a variable number of papillary muscles (usually three) arising from the apical one third of the interventricular septum. The chordae tendineae of the septal leaflet attach directly to small ridges on the interventricular septum.

PATHOLOGY

The histologic lesions of chronic degenerative tricuspid valve disease are qualitatively similar to the myxomatous changes already described in the mitral valve.[4] The tricuspid valve is less frequently affected, and the lesions tend to be less severe and progress less rapidly than those of the mitral valve.[31] The septal cusp of the tricuspid valve is almost always more severely affected than the mural cusp and, when ruptured chordae tendineae are observed in the right side of the heart, those of the septal leaflet are usually affected (see Fig. 25–1).[4, 31, 126] The absence of jet lesions and the difficulty in subjectively assessing right ventricular size make the clinical significance of valvular lesions observed at necropsy hard to interpret in some cases.[4]

PATHOPHYSIOLOGY

In accordance with Gorlin's hydraulic equation, the volume of tricuspid regurgitation varies with the extent of tricuspid valve damage, the degree of right ventricular enlargement, and the magnitude of pulmonary artery pressure.[89] Right atrial pressure tends to increase with increasing regurgitant volume, and signs of congestive heart failure tend to develop when mean right atrial pressure exceeds 10 to 12 mmHg. Gradually developing tricuspid regurgitation is often well tolerated, and right atrial pressure may remain close to normal because of the increased compliance of an enlarged right atrium.

Severe tricuspid regurgitation and heart failure are most likely to develop when organic tricuspid valvular disease is accompanied by pulmonary hypertension. Consequently, right-sided heart failure is seen most often in dogs with CDVD affecting both atrioventricular valves.[210, 211] The modest elevations of pulmonary artery pressure recorded in most dogs with advanced mitral regurgitation (40 to 45 mmHg) are unlikely to result in significant tricuspid regurgitation when the tricuspid valve is anatomically normal. However, even modest elevations of pulmonary artery pressure can cause dramatic increases in tricuspid regurgitant volume in dogs with a pre-existing tricuspid valve leak.

Dilation of the right ventricle induced by pulmonary hypertension from any cause contributes to progressive stretching of the tricuspid annulus, enlargement of the regurgitant orifice, and progressive tricuspid regurgitation. Substantial tricuspid regurgitation flow may develop in the absence of tricuspid valve pathology when the mean pulmonary artery pressure exceeds 60 mmHg.[211] It is interesting that tricuspid regurgitation is slight in most dogs with heartworm disease, even when pulmonary hypertension is severe.[212] Presumably this is because the tricuspid valve is structurally intact and the regurgitant orifice is small. Severe tricuspid regurgitation is more consistently present in dogs with heartworm caval syndrome.[213] This may be due to the combined effects of severe pulmonary hypertension, more pronounced right-sided heart dilatation, and/or mechanical interference with valve closure by the worms in this location. Tricuspid regurgitation is also modest in the majority of dogs and cats with dilated cardiomyopathy. It tends to worsen with the onset of atrial fibrillation due to the loss of atrioventricular synchrony.

HISTORY AND CLINICAL SIGNS

Isolated, organic tricuspid regurgitation is often well tolerated for long periods of time. Ascites, lethargy, and exercise intolerance may develop in severely affected dogs with long-standing tricuspid valve regurgitation. Such signs are often accompanied by muscle wasting, weight loss, anorexia, and, in some cases,

chronic diarrhea. Signs of right-sided heart failure develop more rapidly and are more pronounced in dogs and cats with concurrent left-sided heart failure and/or pulmonary hypertension. When dogs with combined mitral and tricuspid valve disease develop right-sided heart failure, any prior signs of left-sided heart failure usually resolve.[210] Instead, these dogs often suffer marked ascites, profound exercise intolerance, weakness, collapse, or syncope. Dogs with heart failure due to heartworms usually develop exercise intolerance and ascites, but pleural effusion is uncommon.[212] Cats with severe myocardial disease often develop pulmonary hypertension, tricuspid regurgitation, and pleural effusion.

PHYSICAL EXAMINATION

The most reliable physical evidence of tricuspid regurgitation is the combined presence of a typical murmur, jugular vein distention, and a prominent jugular venous pulse. These findings are often overlooked by examiners who neglect to listen on both sides of the thorax and who fail to examine the jugular veins routinely. The murmur is usually holosystolic, of mixed frequency, and loudest at the right 4th intercostal space, just above the costochondral junction.[121] Coexisting mitral regurgitation can mimic or obscure the murmur of tricuspid regurgitation. A heart murmur may be absent in some animals with substantial tricuspid regurgitation even when pulmonary hypertension is present. Obvious jugular distention, hepatomegaly, and ascites can usually be detected in dogs with overt right-sided heart failure. With less severe disease, distended jugular veins with systolic pulsations may be evident only following exercise or when the abdomen is compressed (positive *hepatojugular reflex*).

ELECTROCARDIOGRAPHY

Right atrial and right ventricular enlargement are most likely to be recorded on the ECG when tricuspid regurgitation occurs secondary to chronic pulmonary hypertension. The mean electrical axis is often shifted to the right (> 100° in the dog), and S waves are recorded in leads I, II, III, aVF, and the left-sided chest leads.[126, 127] P-wave amplitude may be increased, but this finding is neither sensitive nor specific. These changes are generally less dramatic or absent in dogs or cats with isolated tricuspid regurgitation because right ventricular hypertrophy is often milder. Coexisting left ventricular enlargement usually obscures the ECG manifestations of right ventricular enlargement.

RADIOGRAPHY

On the dorsoventral projection, moderate to severe right atrial enlargement appears as a bulge on the right craniolateral border of the cardiac silhouette (from 9 to 12 o'clock) (see Figs. 7–1, 7–4, 7–6, 7–7; 25–1). As the right ventricle enlarges, the entire border of the heart becomes more rounded, and the transverse and craniocaudal dimensions of the cardiac silhouette are increased. The distance separating the heart from the right thoracic wall may be diminished, but the value of this sign depends on the position of the cardiac apex (chapter 7). With more pronounced right-sided heart enlargement, the cardiac silhouette may assume a reversed "D" shape. On the lateral radiograph, the dorsoventral dimension of the heart enlarges and the anterior border of the heart becomes more convex (see Figs. 7–1, 7–4, 7–6, 7–7; 25–1). As a result, there is increased contact between the heart and sternum. An enlarged posterior vena cava, hepatomegaly, and ascites support the radiographic diagnosis of right-sided heart enlargement in affected dogs.[214]

CARDIAC CATHETERIZATION

Tricuspid regurgitation is characterized by "ventricularization" of the right atrial pressure tracing.[89] Initially, the normal *x* descent in the right atrial pressure tracing is interrupted by a regurgitant *c-v* wave that commences with the onset of ventricular systole. With more severe tricuspid regurgitation, the right atrial pressure tracing begins to resemble the right ventricular pressure tracing. Signs of right-sided heart failure are usually evident when mean right atrial pressure exceeds 10 to 12 mmHg. When the right atrium is markedly enlarged and very compliant, the atrial pressure tracing may be nearly normal even with moderate to severe regurgitation. Effective (forward) cardiac output declines only when pulmonary vascular resistance is increased or when tricuspid regurgitation is particularly severe.

Right ventricular and pulmonary artery pressure measurements help determine the cause of tricuspid valvular insufficiency. Right ventricular and pulmonary artery systolic pressures are normal or only slightly elevated with isolated structural tricuspid valve disease.[215, 216] The finding of pulmonary hypertension indicates that tricuspid regurgitation is, to some degree, of a functional nature. The amount of tricuspid regurgitation can be roughly quantified by angiocardiographic or indicator dilution techniques.[89, 217] Both methods are plagued by the occurrence of spurious regurgitation induced by arrhythmia or the physical presence of the catheter. These artifacts can be minimized by the use of specially designed catheters, or avoided altogether by performing Doppler echocardiography.[217, 218]

ECHOCARDIOGRAPHY

Doppler echocardiography is the most sensitive and reliable noninvasive clinical technique for identifying tricuspid regurgitation (see Fig. 8–18).[218] A substantial

percentage of healthy dogs have a mild degree of tricuspid regurgitation when the heart is carefully interrogated by pulsed wave or color flow Doppler echocardiography.[124, 152, 219] Healthy human subjects also have small tricuspid valve leaks, and their prevalence increases with age.[218] These small leaks in the valve are inconsequential given the normally low systolic pressures in the right side of the heart. When tricuspid regurgitation is severe, Doppler studies show systolic blood flow reversal in the caudal vena cava and hepatic veins. Doppler techniques have replaced the use of contrast echocardiography (see discussion following).[220, 221] For the same regurgitant volume, the area of a tricuspid jet will be less than that of a mitral jet—unless RV systolic pressures are increased to systemic levels. For this reason, the clinical significance of tricuspid regurgitation on a color flow Doppler echocardiogram is sometimes difficult to assess, and such studies must be interpreted cautiously.

Estimation of the transvalvular pressure gradient using spectral Doppler should be performed whenever a substantial degree of tricuspid regurgitation is observed. Jet velocities in patients with organic tricuspid regurgitation and without pulmonary hypertension are usually less than 2.67 m/sec.[218] Higher velocities indicate pulmonic stenosis or pulmonary hypertension. The systolic pressure gradient is calculated from the peak velocities in the regurgitant jet using the simplified Bernoulli equation ($\Delta P = 4V^2$). Right ventricular (and pulmonary artery) systolic pressure can be quickly calculated if right atrial pressure is known or can be reasonably estimated (central venous pressure measurement). Right ventricular and pulmonary artery systolic pressures estimated in this fashion correlate very well with catheter-derived pressure estimates.[218]

Contrast echocardiography is a valuable and sensitive method for assessing tricuspid regurgitation when Doppler echocardiography is unavailable (chapter 8).[220–222] With this technique, air-agitated saline, dextrose, or indocyanine green dye is injected into a cephalic vein, and the resulting microcavitations, or "bubbles," are followed through the circulation. These bubbles may be observed to travel back and forth across the incompetent tricuspid valve and may reflux into the posterior vena cava or hepatic veins during ventricular systole. False-positive studies can result from arrhythmia, pericardial disorders, and right-sided heart failure.[218]

M-mode and two-dimensional echo findings reflect right ventricular volume overload and are not specific for tricuspid regurgitation. The right ventricle is dilated, and the interventricular septum moves paradoxically toward the transducer and the right ventricle at the onset of systole.[218, 223] During diastole, the interventricular septum is displaced toward the left ventricular cavity as a result of increased filling of the right ventricle. This deformation of the septum is rapidly abolished at the onset of isovolumetric systole when the septum moves rapidly back toward the right ventricle. This motion is paradoxic in the sense that the interventricular septum normally moves away from the transducer toward the contracting left ventricular free wall. Two-dimensional echo also allows assessment of tricuspid valve morphology and motion (prolapse), right ventricular and right atrial size, and evaluation of the pulmonary arteries and caudal vena cava. In dogs with organic tricuspid regurgitation, the septal leaflet is often thickened and may prolapse dorsally into the right atrium during systole.

THERAPY

Treatment of dogs with combined mitral and tricuspid valve disease is essentially the same as that outlined for the management of mitral regurgitation.[210] Tricuspid regurgitation may lessen or disappear when left-sided heart function improves. In dogs and cats with refractory right-sided heart failure, it is often necessary to perform periodic abdominocentesis. Other treatment alternatives include combining diuretics with differing mechanisms of action (furosemide, a thiazide, and/or spironolactone), or administering a venous vasodilator (nitroglycerin or isosorbide dinitrate). The propensity for low-output failure to develop in these animals mandates that diuretic and vasodilator therapy be carefully monitored. Surgical repair of the tricuspid valve should not be attempted prior to repair of the mitral valve when both valves are insufficient. Severe pulmonary edema can result if the tricuspid valve is repaired and the mitral valve is grossly incompetent.[89]

Dogs with isolated tricuspid regurgitation may be asymptomatic for years. Should heart failure develop, it can be effectively managed in most cases using digoxin, diuretics, and/or a low sodium diet. If the right side of the heart is very dilated, it may be helpful to reduce regurgitant volume by performing plication or ring annuloplasty.[89, 224, 225] Such treatment may also be effective in some dogs with functional tricuspid regurgitation. Valve replacement is an effective but costly remedy available at some institutional practices.[89, 167, 226] Long-term improvement in dogs with right-sided heart failure and tricuspid regurgitation due to chronic heartworm infection is dependent on successful adulticide therapy and subsequent remodeling of the pulmonary vasculature (chapter 30). Rest, diuretics, and abdominocentesis are used to alleviate congestion in the interim.

PULMONIC AND AORTIC VALVE INSUFFICIENCY

PULMONIC REGURGITATION

Dilation of the main pulmonary artery and the pulmonic valve ring secondary to chronic pulmonary hy-

pertension is the most important cause of pulmonic valve insufficiency.[5, 89] Iatrogenic pulmonic insufficiency often develops when surgery or balloon valvuloplasty is performed in patients with pulmonic stenosis, but it is usually mild and clinical sequela are rare. Pulmonic valve insufficiency can also occur when the pulmonary artery is dilated from a left-to-right shunting patent ductus arteriosus. Idiopathic pulmonary artery dilatation is an uncommon cause of pulmonic valve insufficiency in dogs.[5, 227] Acquired structural disease of the pulmonic valve leaflets is rare in dogs and cats.

PHYSICAL EXAMINATION

Isolated pulmonic regurgitation characteristically produces a low-pitched, early to mid-diastolic decrescendo or crescendo-decrescendo murmur that is heard best over the pulmonic valve area on the left 3rd or 4th interspace. A systolic murmur is sometimes heard at this same location due either to the ejection of a larger than normal stroke volume or to turbulence generated by eddy currents in the dilated pulmonary artery. On occasion, pulmonic regurgitation is silent—no murmur is detectable. When pulmonic regurgitation develops secondary to pulmonary hypertension, the murmur is usually louder and higher pitched and tends to occur earlier in diastole.[89] This murmur is referred to as a *Graham Steel's murmur* in human patients. Gallop heart sounds, exercise intolerance, and right-sided CHF are common findings in dogs or cats with pulmonary hypertension, but they are uncommon in dogs with isolated pulmonic insufficiency.

ELECTROCARDIOGRAPHY AND RADIOGRAPHY

The ECG manifestations of right ventricular enlargement are modest or absent in dogs with primary valvular insufficiency. They are more reliably present when chronic pulmonary hypertension is the proximate cause of the valve leak. An enlarged right ventricle and pulmonary artery segment are usually observed on thoracic radiographs. In many cases, the proximal portions of the right and left pulmonary arteries are also enlarged.

ANGIOCARDIOGRAPHY AND ECHOCARDIOGRAPHY

Although cardiac catheterization and angiocardiography can help measure right-sided heart and pulmonary artery pressures and demonstrate regurgitation of contrast material into the right ventricle,[89] the diagnosis of pulmonic regurgitation is most easily confirmed by color flow Doppler echocardiography.[228] As with other valve lesions, the severity of regurgitation can be estimated by qualitative or quantitative measurements.[228] More importantly, spectral Doppler interrogation of the regurgitant jet during diastole can provide an accurate estimation of diastolic pulmonary artery pressure, allowing recognition and quantification of pulmonary hypertension (using the modified Bernoulli equation, chapter 8). In patients without pulmonary hypertension, the peak velocity of the regurgitating blood is less than 1.9 m/sec (higher velocities generally indicate pulmonary hypertension). The peak velocity of blood flow through the pulmonic valve orifice during systole may be modestly elevated (2.0 to 2.5 m/sec) due to ejection of an increased stroke volume. Two-dimensional and M-mode echocardiography reveal changes consistent with volume overload of the right side of the heart and, occasionally, diastolic fluttering of the tricuspid valve.[89, 228]

Treatment of isolated pulmonic insufficiency is rarely necessary. In dogs and cats with pulmonary hypertension, treatment is directed at the primary disorder (see chapters 30, 31, and 33).

AORTIC REGURGITATION

When infectious etiologies are excluded (chapter 26), acquired diseases of the aortic valve are very uncommon in dogs and cats. Small jets of aortic insufficiency are often discovered by color flow Doppler echocardiography in older dogs with chronic degenerative valvular disease, presumably as a result of mild myxomatous changes in the aortic valve leaflets.[1–4] Such lesions rarely, if ever, cause an audible murmur or clinical disability. Idiopathic dilation of the aorta is another uncommon cause of aortic insufficiency. It is observed most often in aged dogs and cats. Iatrogenic aortic regurgitation has also been reported as a rare sequela to cardiac puncture and cardiac catheterization.[5, 131] Aortic regurgitation occurs most often in dogs with bacterial endocarditis or in association with congenital heart defects such as ventricular septal defect, tetralogy of Fallot, or discrete fibrous subaortic stenosis (chapter 24).[229, 230] The clinical features and therapy of aortic regurgitation are discussed in chapter 26.

References

1. Detweiler DK, Patterson DF. The prevalence and types of cardiovascular disease in dogs. Ann NY Acad Sci 127:481, 1965
2. Detweiler DK, Luginbuhl H, Buchanan JW, et al. The natural history of acquired cardiac disability in the dog. Ann NY Acad Sci 147:318, 1968
3. Bretschneider J. Zur Pathologie und Pathogenese der

Sogenannten Endocarditis Valvularis Chronica Fibrosa des Hundes. Dissertation, University of Giessen, Germany, 1962
4. Buchanan JW. Valvular disease (endocardiosis in dogs). Adv Vet Sci Comp Med 21:75, 1979
5. Sisson D. Acquired valvular heart disease. *In* Bonagura JD (ed): Contemporary Issues in Small Animal Practice. Cardiology. New York, Churchill Livingstone, 1987, p 59
6. Tashjian RJ, Das KM, Palich KM, et al. Studies on cardiovascular disease in the cat. Ann NY Acad Sci 127:581, 1965
7. Liu S-K, Tashjian RJ, Patnaik AK. Congestive heart failure in the cat. J Am Vet Med Assoc 156:1319, 1970
8. Liu S-K, Tilley LP, Lord PF. Feline cardiomyopathy. *In* Roy PE, Rona G (eds): Recent Advances in Studies on Cardiac Structure and Metabolism. Vol 110. Baltimore, University Park Press, 1975, p 627
9. Liu S-K, Tilley LP. Animal modes of primary myocardial disease. Yale J Biol Med 53:191, 1980
10. Tilley LP, Liu S-K, Gilbertson SR, et al. Primary myocardial disease in the cat. Am J Pathol 87:493, 1977
11. Liu S-K. Pathology of feline heart disease. Vet Clin North Am 7:323, 1977
12. Harpster NK. Feline arrhythmias: diagnosis and management. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 732
13. Fenoglio JJ, Tuan DP, Wit AL, et al. Canine mitral complex. Circ Res 31:417, 1972
14. Perloff JD, Roberts WC. The mitral apparatus. Functional anatomy of mitral regurgitation. Circulation 46:227, 1972
15. Frater RWM, Ellis FH. The anatomy of the canine mitral valve. J Surg Res 1:171, 1961
16. Anderson RH, Wilcox BR. The anatomy of the mitral valve. *In* Wells FC, Shapiro LM (eds): Mitral Valve Disease. 2nd ed. London, Butterworths, 1996, p 4
17. Evans HE. The heart and arteries. *In* Evans HE (ed): Miller's Anatomy of the Dog. 3rd ed. Philadelphia, WB Saunders, 1993, p 586
18. Sonnenblick EH, Napolitano LM, Daggett WM, et al. An intrinsic neuromuscular basis for mitral valve motion in the dog. Circulation 21:9, 1967
19. Priola DY, Fellow C, Moosehouse J, et al. Mechanical activity of canine mitral valve *in situ*. Am J Physiol 219:1647, 1970
20. Wit AL, Fenoglio JJ, Wagner BM, et al. Electrophysiological properties of cardiac muscle in the anterior mitral valve leaflet and the adjacent myocardium in the dog. Circ Res 32:731, 1973
21. von Racknitz W. Inaugural dissertation. Veterinar-Pathologischen Institut der Universität, Munich, Germany, 1964
22. Silverman M, Hurst WJ. The mitral complex. Am Heart J 76:399, 1968
23. Crawley IS, Morris DC, Silverman BD. Valvular heart disease. *In* Hurst JW, Loque RB, Schlant RC, et al (eds): The Heart. 4th ed. New York, McGraw-Hill, 1978, p 992
24. Anderson RH, Wilson BR. The anatomy of the mitral valves. *In* Wells FC, Shapiro LM (eds): Mitral Valve Disease. 2nd ed. London, Butterworths, 1996, p 4
25. Edwards JE, Burchell HB. Pathologic anatomy of mitral regurgitation. Mayo Clin Proc 33:497, 1958
26. Das KM, Patnaik AK, Liu S-K, et al. Cardiovascular pathology of the dog and cat: a case study of 1000 consecutive necropsies. J Am Vet Med Assoc 147:1648, 1965
27. Olson EGJ, Al-Rufare HK. The floppy mitral valve. Br Heart J 44:674, 1980
28. Malcolm AD. Mitral valve prolapse associated with other disorders. Causal coincidence, common link, or fundamental genetic disturbance? Br Heart J 53:353, 1985
29. Mann JM, Davies MJ. The pathology of the mitral valve. *In* Wells FC, Shapiro LM (eds): Mitral Valve Disease. 2nd ed. London, Buutterworths, 1996, p 16
30. Hickey AJ, Wilcken DEL, Wright JS, et al. Primary (spontaneous) chordal rupture: relationship to myxomatous valve disease and mitral valve prolapse. J Am Coll Cardiol 5:1341, 1985
31. Whitney JC. Observations of the effect of age on the severity of heart valve lesions in the dog. J Small Anim Pract 15:511, 1974
32. Kogure K. Pathology of chronic mitral valvular disease in the dog. Jpn J Vet Sci 42:323, 1980
33. Luginbuhl H, Detweiler DK. Cardiovascular lesions in dogs. Ann NY Acad Sci 127:5, 1965
34. Das KM, Tashjian RJ. Chronic mitral valve disease in the dog. Vet Med Small Anim Clin 60:1209, 1965
35. Pensinger RR. Comparative aspects of mitral valve disease in dogs. Ann NY Acad Sci 118:525, 1965
36. Pirie HM. The pathology of heart disease in the dog. J Small Anim Pract 8:175, 1967
37. Jones TC, Zook BC. Aging changes in the vascular system of animals. Ann NY Acad Sci 127:671, 1965
38. Pomerance A. Pathogenesis of senile nodular sclerosis of the anteroventricular valves. Br Heart J 28:815, 1966
39. Pomerance A. Aging changes in human heart valves. Br Heart J 29:222, 1969
40. Pomerance A, Whitney JC. Heart valve changes common to man and dog: a comparative study. Cardiovasc Res 4:61, 1970
41. Angrist A. Aging heart valves and a unitary pathological hypothesis for sclerosis. J Gerontol 19:135, 1964
42. Sokkar SM, Trautwein G. Die Endokardiose der Atrioventrickularklappen des Hundes. I. Morphologische und histochemische Untersuchungen. 261 Vet Med 17A:757, 1970
43. Sokkar SM, Trautwein G. Die Endokardiose der Atrioventrickularklappen des Hundes. II. Papier und immunelektrohoretische Untersuchungen. 261 Vet Med 18A:1, 1971
44. Ernst E, Schneider P, Trautwein G. Die Endokcardiose der Atrioventrickularklappen des Hundes. IV. Electronmikroskopische Untersuchungen. 261 Vet Med 21A:400, 1974
45. Schneider PE, Ernst E, Trautwein G. Die Endokardiose der Atrioventrickularklappen des Hundes. III. Enzymhistochemische Untersuchungen. 261 Vet Med 19A:809, 1972
46. Schole J. Untersuchungen zur atiologic and pathogenese der Endokardiose and Endokarditis des Hundes. IV. Biochemische Untersuchungen. Dtsch Tiergerztl Wochensch 80:472, 1973
47. Fenoglio JJ, Wagner BM. Connective tissue and control of cardiac function. Pathobiol Ann 4:199, 1974
48. Schneider P, Ernst E, Trautwein G. Amyloidose der Herzklappen beim Hund. Vet Pathol 8:130, 1971
49. Ernst E, Schneider P, Trautwein G. Elecktronen mikroskopische Untersuchungen uber die Amyloidose der Atrioventrickularklappen des Hundes. Beitr Pathol Bd 152:361, 1974
50. Jonsson L. Coronary arterial lesions and myocardial infarcts in the dog. Acta Vet Scand Suppl 38:5, 1972
51. King BD, Clark MA, Mobushis B, et al. "Myxomatous" mitral valves: collagen dissolution as the primary defect. Circulation 66:288, 1982
52. Kuivaniemi H, Tromp G, Prockop DJ. Mutations in

fibrillar collagens (types I, II, III, and XI), fibril-associated collagen (type IX), and network-forming collagen (type X) cause a spectrum of diseases of bone, cartilage, and blood vessels. Hum Mutat 9:300, 1997
53. Bashey RI, Bashey HM, Jimenez SA. Characterization of pepsin-solubilized bovine heart-valve collagen. Biochem J 73:885, 1978
54. Jaffe AS, Geltman EM, Rodey GE. Mitral valve prolapse: a consistent manifestation of type IV Ehlers-Danlos syndrome. Circulation 64:121, 1981
55. Hammer D, Leier CV, Baba N. Altered collagen composition in a prolapsing mitral valve with ruptured chordae tendineae. Am J Med 67:863, 1979
56. Byera PH. Disorders of collagen biosynthesis and structure. *In* Scriver CR, Beaudet AL, Sly WA, et al (eds): The Metabolic and Molecular Bases of Inherited Disease. New York, McGraw-Hill, 1995, p 4029
57. Davis MJ, Moore BP, Braimbridge MV. The floppy mitral valve. Study of incidence, pathology and complications in surgical, necropsy and forensic material. Br Heart J 40:468, 1978
58. Cole WG, Chan D, Hickey AJ, et al. Collagen composition of normal and myxomatous human mitral heart valves. Biochem J 219:451, 1984
59. Caulfield JB, Page DL, Kastor JA, et al. Connective tissue abnormalities in spontaneous rupture of chordae tendineae. Arch Pathol 91:537, 1971
60. Jeresaty RM, Edwards JE, Surendra KC. Mitral valve prolapse and ruptured chordae tendineae. Am J Cardiol 55:138, 1985
61. Birkdal-Hansen H, Moore WGI, Bodden MK, et al. Matrix metalloproteinases: a review. Crit Rev Oral Biol Med 4:197, 1993
62. Shingleton WD, Hodges DJ, Brick P, et al. Collagenase: a key enzyme in collagen turnover. Biochem Cell Biol 74:759, 1996
63. Tamura K, Fukuda Y, Ishizaki M, et al. Abnormalities in elastic fibers and other connective-tissue components of floppy mitral valve. Am Heart J 129:1149, 1995
64. Pyeritz RE. Disorders of fibrillin and microfibrillogenesis: Marfan syndrome, MASS phenotype, contractural arachnodactyly and related conditions. *In* Rimoin DL, Connor JM, Pyeritz RE (eds): Principles and Practice of Medical Genetics. 3rd ed. New York, Churchill Livingstone, 1996, p 183
65. Jacobs GJ, Calvert CA, Mahaffey MB, et al. Echocardiographic detection of flail left atrioventricular valve cusp from ruptured chordae tendineae in 4 dogs. J Vet Intern Med 9:341, 1995
66. Schneider P, Ernst E, Trautwein G, et al. Experimentelle durch ACTH und DOC induzierte herzklappenendokardiose. Endokrinologie 62:215, 1973
67. Slavin J, Unemori E, Hunt TK, et al. Transforming growth factor-beta (TGF-beta) and dexamethasone have direct opposing effects on collagen metabolism in low passage human dermal fibroblasts in vitro. Growth Factors 11:205, 1994
68. Brilla CG, Rupp H, Funck R, et al. The renin-angiotensin-aldosterone system and myocardial collagen matrix remodelling in congestive heart failure. Eur Heart 16(Suppl O):107, 1995
69. Harpster NK. Cardiovascular diseases of the domestic cat. Adv Vet Sci Comp Med 21:39, 1977
70. Stunzi H. Aur Pathogenese der Endocarditis valvularis. Schweiz Arch Tierheilk 104:135, 1962
71. Thrusfield MV, Aitken CGG, Darke PGG. Observations on breed and sex in relation to canine heart valve incompetence. J Small Anim Pract 26:709, 1985
72. Darke PGG. Valvular incompetence in Cavalier King Charles spaniels. Vet Rec 120:365, 1987
73. Häggström J, Hansson K, Karlberg BE, et al. Chronic valvular disease in the cavalier King Charles spaniel in Sweden. Vet Rec 131:549, 1992
74. Beardow AW, Buchanan JW. Chronic mitral valve disease in Cavalier King Charles spaniels: 95 cases (1987–1991). J Am Vet Med Assoc 203:1023, 1993
75. Malik R, Hunt GB, Allan GS. Prevalence of mitral valve insufficiency in cavalier King Charles spaniels. Vet Rec 130:302, 1992
76. Braunwald E, Welch GH, Sarnoff SJ. Hemodynamic effects of quantitatively varied experimental mitral regurgitation. Circ Res 5:539, 1957
77. Braunwald E. Mitral regurgitation. Physiologic, clinical and surgical considerations. N Engl J Med 281:425, 1969
78. Urschel CW, Covell JW, Graham TP, et al. Effects of acute valvular regurgitation on the oxygen consumption of the canine heart. Circ Res 23:33, 1968
79. Urschel CW, Covell JW, Sonnenblick EH, et al. Myocardial mechanics in aortic and mitral valvular regurgitation: the concept of instantaneous impedance as a determinant of the performance of the intact heart. J Clin Invest 17:867, 1968
80. Graham TP, Covell JW, Sonnenblick KH, et al. Control of myocardial oxygen consumption: relative influence of contractile state and tension development. J Clin Invest 47:375, 1968
81. Taylor RR, Cingolani HE, Graham TP. Myocardial oxygen consumption, left ventricular fiber shortening and wall tension. Cardiovasc Res 1:219, 1967
82. Yoran C, Yellin EL, Becker RM, et al. Dynamic aspects of acute mitral regurgitation: effects of ventricular volume, pressure and contractility on the effective regurgitant area. Circulation 60:170, 1979
83. Yoran C, Yellin EL, Hori M, et al. Effects of heart rate on experimentally produced mitral regurgitation in dogs. Am J Cardiol 152:134, 1983
84. Pierpont GL, Tulley RC. Pathophysiology of valvular heart disease. The dynamic nature of mitral valve regurgitation. Arch Intern Med 142:998, 1982
85. Sasayama S, Takahashi M, Osakada G, et al. Dynamic geometry of the left atrium and left ventricle in acute mitral regurgitation. Circulation 60:177, 1979
86. Yellin EL, Yoran C, Sonnenblick EH, et al. Dynamic changes in the canine mitral regurgitant orifice area during ventricular ejection. Circ Res 45:677, 1979
87. Yoran C, Yellin EL, Gabbay S, et al. Mechanism of reduction of mitral regurgitation with vasodilator therapy. Am J Cardiol 43:773, 1979
88. Greenberg BH, Massie BM, Brundage BH, et al. Beneficial effects of hydralazine in severe mitral regurgitation. Circulation 58:273, 1978
89. Braunwald E. Valvular heart disease. *In* Braunwald E (ed): Heart Disease, A Textbook of Cardiovascular Medicine. 5th ed. Philadelphia, WB Saunders, 1997, p 1007
90. Kihara Y, Sasayama S, Miyazaki S, et al. Role of the left atrium in adaptation of the heart to chronic mitral regurgitation in conscious dogs. Circ Res 62:543, 1988
91. Sisson D, Brown W. Hemodynamic effects of atrial fibrillation in dogs with experimentally induced mitral regurgitation. Abstract. J Vet Intern Med 9:200, 1995
92. Ware WA, Lund DD, Subieta AR, et al. Sympathetic activation in dogs with congestive heart failure caused by chronic mitral valve disease and dilated cardiomyopathy. J Am Vet Med Assoc 197:1475, 1990
93. Häggström J, Hansson K, Karlberg BE, et al. Effects of

long-term treatment with enalapril or hydralazine on the renin-angiotensin-aldosterone system and fluid balance in dogs with naturally acquired mitral valve regurgitation. Am J Vet Res 57:1645, 1996
94. Häggström J, Hansson K, Karlberg BE, et al. Plasma concentration of atrial natriuretic peptide in relation to severity of mitral regurgitation in Cavalier King Charles Spaniels. Am J Vet Res 55:698, 1994
95. Pedersen HD. Effects of mild mitral valve insufficiency, sodium intake, and place of blood sampling on the renin-angiotensin system in dogs. Acta Vet Scand 37:109, 1996
96. Pedersen HD, Koch J, Poulsen K, et al. Activation of the renin-angiotensin system in dogs with asymptomatic and mildly symptomatic mitral valvular insufficiency. J Vet Intern Med 9:328, 1995
97. Häggström J. Chronic valvular disease in Cavalier King Charles Spaniels: epidemiology, inheritance, and pathophysiology. Thesis. Uppsala University, Uppsala, Sweden, 1996
98. Häggström J, Hansson K, Kvart C, et al. Effects of naturally acquired decompensated mitral valve regurgitation on the renin-angiotensin-aldosterone system and atrial natriuretic peptide concentration in dogs. Am J Vet Res 58:77, 1997
99. Takemura N, Koyama H, Sako T, et al. Atrial natriuretic peptide in the dog with mitral regurgitation. Res Vet Sci 50:86, 1991
100. Zile MR, Gaasch WH, Carroll JD, et al. Chronic mitral regurgitation: predictive value of preoperative echocardiographic indexes of left ventricular function and wall stress. J Am Coll Cardiol 3:235, 1984
101. Borow KM, Green LH, Mann T, et al. End-systolic volume as a predictor of postoperative left ventricular performance in volume overload from valvular regurgitation. Am J Med 68:655, 1980
102. Kotler MN, Mintz GS, Parry WR, et al. M-mode and 2-dimensional echocardiography in mitral and aortic regurgitation: pre- and postoperative evaluation of volume overload of the left ventricle. Am J Cardiol 46:144, 1980
103. Schuler G, Peterson KL, Johnson A, et al. Temporal response of left ventricular performance to mitral valve surgery. Circulation 59:1218, 1979
104. Grossman W. Aortic and mitral regurgitation. How to evaluate the condition and what to consider surgical intervention. J Am Med Assoc 252:2447, 1984
105. Kittleson MD, Eyster GE, Knowlen GG. Myocardial function in small dogs with chronic mitral regurgitation and severe congestive heart failure. J Am Vet Med Assoc 184:455, 1984
106. Prasad K, O'Neil CL, Bharadwa MB. Effects of chronic digoxin treatment on cardiac function, electrolytes, and sarcolemmal ATPase in the canine failing heart due to chronic mitral regurgitation. J Am Med Assoc 108:1487, 1984
107. Carabello BA, Nakano K, Corin W, et al. Left ventricular function in experimental volume overload hypertrophy. Am J Physiol 256:H974, 1989
108. Kleaveland JP, Kussmaul WG, Vinciguerra T, et al. Volume overload hypertrophy in a closed-chest model of mitral regurgitation. Am J Physiol 254:H1034, 1988
109. Carabello BA, Nakano K, Ishihara K, et al. Coronary blood flow in dogs with contractile dysfunction due to experimental volume overload. Circulation 83:1063, 1991
110. Urabe Y, Mann DL, Kent RL, et al. Cellular and ventricular contractile dysfunction in experimental canine mitral regurgitation. Circ Res 70:131, 1992
111. Katz AM. The cardiomyopathy of overload. A major determinant of prognosis in congestive heart failure. N Engl J Med 322:100, 1990
112. Sagawa K, Suga H, Shoukas A, et al. End-systolic pressure/volume ratio: a new index of ventricular contractility. Am J Cardiol 40:748, 1977
113. Nagatsu M, Zile MR, Tsutsui H, et al. Native beta-adrenergic support for left ventricular dysfunction in experimental mitral regurgitation normalizes indexes of pump and contractile function. Circulation 89:818, 1994
114. Kaplan PM, Fox PR, Garvey MS, et al. Acute mitral regurgitation with papillary muscle rupture in a dog. J Am Vet Med Assoc 191:1436, 1987
115. Buchanan JW. Chronic valve disease and left atrial splitting in the dog. Master's Thesis, University of Pennsylvania Graduate School of Medicine, Philadelphia, 1966
116. Ettinger SJ, Suter PF. Acquired valvular and endocardial heart disease. *In* Ettinger SJ, Suter PF: Canine Cardiology. Philadelphia, WB Saunders, 1970, p 321
117. Hamlin RL. Prognostic value of changes in the cardiac silhouette in dogs with mitral insufficiency. J Am Vet Med Assoc 153:1436, 1968
118. Suter PF. Cardiac diseases. *In* Suter PF: Thoracic Radiography. An Atlas of Thoracic Diseases in the Dog and Cat. Wetlswil, Switzerland, Peter F. Suter, 1984, p 351
119. Ettinger SJ. Valvular heart disease. *In* Ettinger SJ (ed): Textbook of Veterinary Medicine; Diseases of the Dog and Cat. 2nd ed. Vol 2. Philadelphia, WB Saunders, 1983, p 956
120. Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for Diagnosis. 6th ed. Boston, Little, Brown, 1964
121. Detweiler DK, Patterson DF. A phonographic record of heart sounds and murmurs of the dog. Ann NY Acad Sci 127:322, 1965
122. Hahn A. Auscultation of the canine patient: Part VI. Murmurs. Small Anim Clin 2:13, 1962
123. Häggström J, Kvart C, Hansson K. Heart sounds and murmurs: changes relate to severity of chronic valvular disease (CVD) in the cavalier King Charles spaniel. J Vet Intern Med 9:75, 1995
124. Darke P, Bonagura JD, Kelly DF. Mitral valve disease. *In* Color Atlas of Veterinary Cardiology. London, Mosby-White, 1996, p 57
125. Lombard CW, Spencer CP. Correlation of radiographic, echocardiographic, and electrocardiographic signs of left heart enlargement in dogs with mitral regurgitation. Vet Rad 26:89, 1985
126. Chen K-Y. Reevaluation and revision of electrocardiographic criteria for the diagnosis of left ventricular hypertrophy in dogs. J Chin Soc Vet Sci 14:359, 1988
127. Tilley LP. Analysis of canine P-QRS-T deflections. *In* Essentials of Canine and Feline Electrocardiography. 3rd ed. Philadelphia, Lea and Febiger, 1992, p 59
128. Häggström J, Hamlin RL, Hansson K, et al. Heart rate variability in relation to severity of mitral regurgitation in Cavalier King Charles spaniels. J Small Anim Pract 37:69, 1996
129. Buchanan JW. Spontaneous arrhythmias and conduction disturbances in domestic animals. Ann NY Acad Sci 127:224, 1965
130. Sellers RD, Levy MJ, Amplatz K, et al. Left retrograde cardioangiography in acquired heart disease: technique, indications, and interpretations in 700 cases. Am J Cardiol 14:437, 1964
131. Buchanan JW. Selective angiography and angiocardiog-

raphy in dogs with acquired cardiovascular disease. Am J Vet Rad 6:5, 1965

132. Lord PF. Left ventricular volumes of the diseased canine heart: congestive cardiomyopathy and volume overload (patent ductus arteriosus and primary valvular insufficiency). Am J Vet Res 35:493, 1974
133. Lord PF. Quantitative left ventricular cineangiocardiography in the dog: measurement and usefulness of left ventricular volume. J Am Vet Rad Soc 18:51, 1977
134. Weyman AE. Left ventricular inflow tract I. *In* Weyman AE: Principles and Practice of Echocardiography. Philadelphia, Lea and Febiger, 1994, p 391
135. Perry GJ, Nanda NC. Recent advances in color Doppler evaluation of valvular regurgitation. Echocardiography 4:503, 1987
136. Nakayama T, Wakao Y, Takiguchi S, et al. Prevalence of valvular regurgitation in normal beagle dogs detected by color Doppler echocardiography. J Vet Med Sci 56:973, 1994
137. Yuill CD, O'Grady MR. Doppler-derived velocity of blood flow across the cardiac valves of normal dogs. Can J Vet Res 55:185, 1991
138. Chen CG, Thomas JD, Anconina J. Impact of impinging wall jet on color Doppler quantification of mitral regurgitation. Circulation 84:712, 1991
139. Hemcke F, et al. Color Doppler assessment of mitral regurgitation with orthogonal planes. Circulation 75:175, 1987
140. Uehara Y, Takahashi M. Quantitative evaluation of the severity of mitral insufficiency in dogs by the color Doppler method. J Vet Med Sci 58:249, 1996
141. Fisher DC, Sahn DJ, Friedman MJ, et al. The mitral valve orifice method for noninvasive two-dimensional echo Doppler determination of cardiac output. Circulation 67:712, 1983
142. Ascah KJ, Stewart WJ, Jiang L, et al. A Doppler two-dimensional echocardiographic method for quantitation of mitral regurgitation. Circulation 72:377, 1985
143. Tribouilloy C, Shen WF, Slama MA, et al. Non-invasive measurement of the regurgitant fraction by pulsed Doppler echocardiography in isolated pure mitral regurgitation. Br Heart J 66:290, 1991
144. Rivera JM, Vandervoort PM, Thoreau DH, et al. Quantification of mitral regurgitation with the proximal flow convergence method: a clinical study. Am Heart J 124:1289, 1992
145. Chen C, Koschyk D, Brockhoff C, et al. Noninvasive estimation of regurgitant flow rate and volume in patients with mitral regurgitation by Doppler color mapping of accelerating flow field. J Am Coll Cardiol 21:374, 1993
146. Shiota T, Jones M, Tiena DE, et al. Evaluation of mitral regurgitation using a digitally determined color flow convergence "centerline" acceleration method. Circulation 89:2879, 1994
147. Schwammenthal E, Chen C, Benning F, et al. Dynamics of mitral regurgitant flow and orifice area. Physiologic application of the proximal flow convergence method: clinical data and experimental testing. Circulation 90:307, 1994
148. Mele D, Vandervoort P, Palacios I, et al. Proximal jet size by Doppler color flow mapping predicts severity of mitral regurgitation. Clinical studies. Circulation 1:746, 1995
149. Frieske R, Engelhard B, Franke A, et al. Transesophageal Doppler echocardiography assessment of mitral valve insufficiency: comparison of jet area, pulmonary venous flow profile, proximal jet diameter, maximal regurgitation flow rate and regurgitation orifice area with angiography. Z Kardiol 86:346, 1997
150. Feigenbaum H. Echocardiography. 5th ed. Malvern, PA, Lea and Febiger, 1994, p 456
151. Pipers FS, Bonagura JD, Hamlin RL, et al. Echocardiographic abnormalities of the mitral valve associated with left-side heart diseases in the dog. J Am Vet Med Assoc 179:580, 1981
152. Kienle RD, Thomas WP. Echocardiography. *In* Nyland TG, Mattoon JS (eds): Veterinary Diagnostic Ultrasound. Philadelphia, WB Saunders, 1995, p 198
153. Pedersen HD, Kristensen BO, Lorentzen KA, et al. Mitral valve prolapse in 3-year-old healthy Cavalier King Charles Spaniels. An echocardiographic study. Can J Vet Res 59:294, 1995
154. Pedersen HD, Kristensen BO, Norby B, et al. Echocardiographic study of mitral valve prolapse in Dachshunds. J Vet Med Assoc 43:103, 1996
155. Nakayama T, Wakao Y, Nemoto H, et al. Mitral valve protrusion assessed by use of B-mode echocardiography in dogs with mitral regurgitation. Am J Vet Res 57:791, 1996
156. Mintz GS, Kotler MN, Segal BL, et al. Two-dimensional echocardiographic recognition of ruptured chordae tendineae. Circulation 57:244, 1978
157. Humphries WC, Hammer WJ, McDonough MT, et al. Echocardiographic equivalents of a flail mitral leaflet. Am J Cardiol 40:902, 1977
158. Child JS, Skorton DJ, Taylor RD, et al. M-mode and cross-sectional echocardiographic features of flail posterior mitral leaflets. Am J Cardiol 44:1383, 1979
159. Vuille C, Weyman AE. Left ventricle I: General considerations, assessment of chamber size and function. *In* Weyman AE (ed): Principles and Practice of Echocardiography. Philadelphia, Lea and Febiger, 1994, p 575
160. Zile MR, Gaasch WH, Carrol JD, et al. Chronic mitral regurgitation: predictive value of preoperative echocardiographic indices of left ventricular function and wall stress. J Am Coll Cardiol 3:325, 1984
161. Zile MR, Gaasch WH, Levine HJ. Left ventricular stress-dimension-shortening relations before and after correction of chronic aortic and mitral regurgitation. Am J Cardiol 56:99, 1985
162. Cohn LH, Couper GS, Aranki SF, et al. Long-term results of mitral valve reconstruction for the regurgitating myxomatous mitral valve. J Thorac Cardiovasc Surg 107:143, 1994
163. Colon R, Frazier OH. Mitral valve replacement techniques. *In* Wells FC, Shapiro LM (eds): Mitral Valve Disease. 2nd ed. London, Butterworths, 1996, p 135
164. Wells FC. Conservation and repair of the mitral valve. *In* Wells FC, Shapiro LM (eds): Mitral Valve Disease. 2nd ed. London, Butterworths, 1996, p 114
165. Boggs LS, Dewan SJ, Ballard SE. Mitral valve reconstruction in a toy-breed dog. J Am Vet Med Assoc 209:1872, 1996
166. Kanemoto I, Shibata S, Noguchi H, et al. Successful mitral valvuloplasty for mitral regurgitation in a dog. Nippon Juigaku Zasshi 52:411, 1990
167. Breznock EM. Tricuspid and mitral valvular disease: valve replacement. Semin Vet Med Surg (Small Anim) 9:234, 1994
168. Keene BW, Rush JE. Therapy of heart failure. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 867
169. Fox PR, Sisson DD. Angiotensin-converting enzyme inhibitors. *In* Bonagura JD (ed): Kirk's Current Veteri-

nary Therapy XII. Small Animal Practice. Philadelphia, WB Saunders, 1995, p 786
170. Cody RJ, Covit AB, Schaer GL, et al. Sodium and water balance in chronic congestive heart failure. J Clin Invest 77:1441, 1986
171. Shimoyama H, Sabbah HN, Roman H, et al. Effects of long-term therapy with enalapril on severity of functional mitral regurgitation in dogs with moderate heart failure. J Am Coll Cardiol 25:768, 1995
172. Hamlin RL, Benitz AM, Ericsson GF, et al. Effects of enalapril on exercise tolerance and longevity in dogs with heart failure produced by iatrogenic mitral regurgitation. J Vet Intern Med 10:85, 1996
173. The COVE Study Group. Controlled clinical evaluation of enalapril in dogs with heart failure: results of the Cooperative Veterinary Enalapril Study Group. J Vet Intern Med 9:243, 1995
174. The IMPROVE Study Investigators. Clinical effects of enalapril maleate in dogs with naturally acquired heart failure: results of the invasive multicenter prospective veterinary evaluation of enalapril. J Vet Intern Med 9:234, 1995
175. Ettinger SJ: ACE inhibitors—why, when, and why not? Proceedings, 15th Annual Vet Med Forum, 1997, p 194
176. Hofmann S, Kersten U. The effectiveness and tolerance of ramipril in comparison to captopril for heart failure in dogs. Dtsch Tierarztl Wochenschr 103:159, 1996
177. Morisse B, Kersten U. Treatment of heart failure in dogs with ACE inhibitors: comparison of quinapril and captopril. Tierarztl Prax 23:489, 1995
178. Pouchelon JL, Benazepril Veterinary Investigators. Treatment of heart failure in dogs with benazepril—results of European double-blind placebo controlled study. Abstract. J Vet Intern Med 10:163, 1996
179. Kittleson MD. The acute hemodynamic effects of captopril in dogs with heart failure. J Vet Pharmacol Ther 16:1, 1993
180. Bright JM. Controversies in veterinary medicine: is the long-term use of digitalis for treatment of low output failure unwarranted? J Am Anim Hosp Assoc 19:233, 1983
181. Kittleson MD, Hamlin RL. Hydralazine therapy for severe mitral regurgitation in a dog. J Am Vet Med Assoc 179:903, 1981
182. Kittleson MD, Johnson LE, Oliver ND. Acute hemodynamic benefits of hydralazine in dogs with chronic mitral regurgitation. J Am Vet Med Assoc 187:258, 1985
183. Kittleson MD, Eyster GE, Oliver NB, et al. Oral hydralazine for chronic mitral regurgitation in the dog. J Am Vet Med Assoc 182:1205, 1983
184. Kittleson MD, Hamlin RL. Hydralazine pharmacodynamics in the dog. Am J Vet Res 44:1501, 1983
185. Rutishauser W. A review of the long-term effects of prazosin and hydralazine in chronic congestive heart failure. Eur Heart J 4:149A, 1983
186. Packer M, O'Connor CM, Ghali JK. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. N Engl J Med 335:1107, 1996
187. Burges RA, Dodd MG, Gardiner DG. Pharmacologic profile of amlodipine. Am J Cardiol 64:101, 1989
188. Yamanaka K, Suzuki M, Ishiko J. Antihypertensive effects of amlodipine, a new calcium antagonist. Nippon Yakurigaku Zasshi 97:115, 1991
189. Packer M. Vasodilator and inotropic therapy for severe chronic heart failure; passion and skepticism. Am Coll Cardiol 2:841, 1983
190. Jugdutt BI, Khan MI. Effect of prolonged nitrate therapy on left ventricular remodeling after canine acute myocardial infarction. Circulation 89:2297, 1994
191. McDonald KM, Francis GS, Matthews J, et al. Long-term oral nitrate therapy prevents chronic ventricular remodeling in the dog. J Am Coll Cardiol 21:514, 1993
192. Jugdott BI, Khan MI, Jugdott SJ, et al. Impact of left ventricular unloading after late reperfusion of canine anterior myocardial infarction on remodeling and function using isosorbide-5-mononitrate. Circulation 92:926, 1995
193. Häggström J, Hansson K, Kvart C, et al. Chronic valvular heart disease in cavalier King Charles spaniels in Sweden. Vet Rec 131:549, 1992
194. Swensen L, Häggström J, Kvart C, et al. Relationship between parental status in Cavalier King Charles Spaniels and severity of chronic valvular disease in offspring (CVD). J Vet Med Assoc 208:2009, 1996
195. Ettinger S, Buergelt CD. Atrioventricular dissociation (incomplete) in the dog with ruptured chordae tendineae. Am J Vet Res 29:1499, 1968
196. Ettinger S, Buergelt CD. Ruptured chordae tendineae in the dog. J Am Vet Med Assoc 155:544, 1969
197. Liu S-K, Suter PF, Ettinger S. Pulmonary alveolar microlithiasis with ruptured chordae tendineae in mitral and tricuspid valves in a dog. J Am Vet Med Assoc 155:1692, 1969
198. Haller J, Morrow A. Experimental mitral insufficiency. An operative method of chronic survival. Ann Surg 142:37, 1955
199. Haller J, Morrow A. Experimental mitral insufficiency. Surgery 38:518, 1955
200. Buchanan JW. Atrioventricular insufficiency and sequela. *In* Kirk RW (ed): Current Veterinary Therapy III. Philadelphia, WB Saunders, 1978, p 205
201. Buchanan JW, Kelly AM. Endocardial splitting of the left atrium in the dog with hemorrhage and hemopericardium. J Am Vet Rad Soc 5:28, 1964
202. Stunzi H, Mann M. Rupture of the atrium. Zeutra 161 Veterinaermed 17A:757, 1970
203. Buchanan JW. Spontaneous left atrial rupture in dogs. *In* Bloor CM (ed): Comparative Pathophysiology of Circulatory Disturbances. Vol 22. New York, Plenum Press, 1976, p 315
204. Komitor DA. Left atrial rupture. Vet Med Small Anim Clin 71:620, 1976
205. Sadanaga KK, MacDonald MJ, Buchanan JW. Echocardiography and surgery in a dog with left atrial rupture and hemopericardium. J Vet Intern Med 4:216, 1990
206. Kersten U. Klinische Untersuchungen am Herzkranken Hund. Thesis, Hannover, Germany, 1968
207. Darke P, Bonagura JD, Kelly DF. Dilated cardiomyopathy. *In* Color Atlas of Veterinary Cardiology. London, Mosby-White, 1996, p 98
208. Jacobs G, Hutson C, Dougherty J, et al. Congestive heart failure associated with hyperthyroidism in cats. J Am Vet Med Assoc 188:52, 1986
209. Higashidate M, Tamiya K, Kurosawa H, et al. Role of the septal leaflet in tricuspid valve closure. Consideration for treatment of complete atrioventricular canal. J Thorac Cardiovasc Surg 104:1212, 1992
210. Takemura N, Koyama H, Motoyoshi S. Congestive heart failure due to bilateral atrioventricular valve insufficiency in two dogs. J Vet Med Sci 58:38, 1996
211. Wallace CR, Hamilton WF. Study of spontaneous congestive heart failure in the dog. Circ Res 11:301, 1962
212. Knight DH. Heartworm heart disease. Adv Vet Sci Comp Med 21:107, 1977
213. Kuwahara Y, Kitagawa H, Sasaki Y, et al. Cardiopulmo-

nary values in dogs with artificial model of caval syndrome in heartworm disease. J Vet Med Sci 53:59, 1991
214. Lehmkuhl LB, Bonagura JD, Biller DS, et al. Radiographic evaluation of caudal vena cava size in dogs. Vet Radiol Ultrasound 38:94, 1997
215. Sepulveda G, Lukas DS. The diagnosis of tricuspid insufficiency. Circulation 11:552, 1955
216. Hansing CE, Rowe GG. Tricuspid insufficiency. A study of hemodynamics and pathogenesis. Circulation 45:793, 1972
217. Ubago JL, Figueroa A, Colman T, et al. Right ventriculography as a valid method for the diagnosis of tricuspid insufficiency. Cathet Cardiovasc Diagn 7:433, 1981
218. Weyman AE. Right ventricular inflow tract. *In* Weyman AE: Principles and Practice of Echocardiography. Philadelphia, Lea and Febiger, 1994, p 824
219. Yuill CDM, O'Grady MR. Doppler-derived velocity of blood flow across the cardiac valves in the normal dog. Can J Vet Res 55:185, 1991
220. Curtis JM, Thyssen M, Breuer HWM, et al. Doppler echocardiography versus contrast echocardiography for diagnosis of tricuspid regurgitation. Abstract. Eur Heart J 5(Suppl 1):213, 1984
221. Curtis JM, Thyssen M, Breur HM, et al. Doppler versus contrast echocardiography for diagnosis of tricuspid regurgitation. Am J Cardiol 56:333, 1985
222. Lieppe W, Behar VS, Sallion R, et al. Detection of tricuspid regurgitation with 2-dimensional echocardiography and peripheral vein injections. Circulation 57:128, 1978
223. deMadron E, Bonagura JD, O'Grady MR. Normal and paradoxical ventricular septal motion in the dog. Am J Vet Res 46:1832, 1985
224. Kirklin JW, Barratt-Boyes BG. Tricuspid valve disease. *In* Cardiac Surgery. 2nd ed. New York, Churchill Livingstone, 1993, p 589
225. Duran CM. Tricuspid valve disease revisited. J Cardiovasc Surg 9(suppl):242, 1994
226. Orton EC. Congenital heart disease in dogs. Proceedings, North American Veterinary Conference 1998, p 85
227. Polzin DJ, Ogburn P. Isolated pulmonary valvular insufficiency in a dog. J Am Anim Hosp Assoc 17:301, 1981
228. Weyman AE. Right ventricular outflow tract. *In* Weyman AE: Principles and Practice of Echocardiography. Philadelphia, Lea and Febiger, 1994, p 824
229. Eyster GE, Anderson LK, Cords GB. Aortic regurgitation in the dog. J Am Vet Med Assoc 168:138, 1976
230. Sisson D, Luethy M, Thomas WP. Ventricular septal defect accompanied by aortic regurgitation in five dogs. J Am Anim Hosp Assoc 27:441, 1991

26

Infectious Endocarditis

MATTHEW W. MILLER
DAVID SISSON

Infectious endocarditis (IE) is an often fatal systemic disease caused by bacterial or, more rarely, fungal infection of the valvular or mural endocardium. Infectious endocarditis occurs infrequently in dogs and rarely in cats. As a result, it is often neglected as a differential diagnosis, with often dire consequences. The diagnosis of IE requires a high index of suspicion, familiarity with the population at risk, and knowledge of the usual patient circumstances in which it occurs. The clinical importance of infectious endocarditis resides in the diagnostic challenge it presents to the clinician, the formidable consequences it imposes on its victims, and the obstacles confronted in treating and preventing this often catastrophic disease.

EPIDEMIOLOGY

The incidence of infectious endocarditis in dogs and cats is not precisely known. Published estimates of its prevalence in dogs range from 0.11 to 0.58 percent.[1–4] Much less is known about the incidence of IE in cats; the bulk of the literature consists of isolated case reports.[5–7] In 1994, Sisson[8] reviewed the epidemiology of IE in dogs and cats based on the evaluation of 10 years of clinical data submitted to the Veterinary Medical Data Base at Purdue; the incidence of IE in dogs was estimated at 0.04 to 0.13 percent of the cases presented for clinical evaluation. This incidence increases with advancing age (Fig. 26–1), and male dogs are at slightly greater risk for infection than female dogs.[8] Breed-related risk factors were slight and probably related to the occurrence of certain predisposing congenital heart defects. In this same report, the incidence of IE in cats was somewhere between 0.006 and 0.018 percent of cats presented for evaluation.[8]

In humans, many pre-existing heart diseases increase the risk of developing bacterial endocarditis, including patent ductus arteriosus, aortic regurgitation, aortic stenosis, mitral regurgitation, mitral stenosis, and ventricular septal defect.[9–11] Several studies have shown that dogs with subvalvular aortic stenosis are predisposed to endocarditis.[2, 8, 12] Endocarditis has also been described in dogs with patent ductus arteriosus and ventricular septal defects, but no relative risk data have been published.[2, 13, 14] It is interesting that there is no published evidence that degenerative valvular disease predisposes dogs to IE.

PATHOLOGY

The characteristic lesion of infective endocarditis is a vegetation. In dogs and cats, as in humans, most vegetative lesions develop on the mitral or

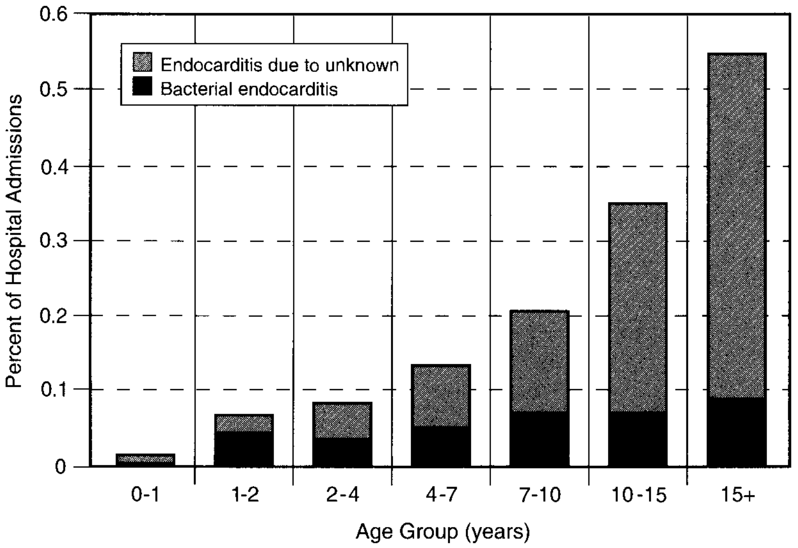


FIGURE 26–1

The prevalence of bacterial endocarditis in dogs increases with advancing age. This graph was constructed from data obtained from the Veterinary Medical Data Base at Purdue University for visits recorded from January, 1984, through May, 1994. The figure shows those cases coded as bacterial endocarditis and those coded as endocarditis due to unknown.

aortic valves or both (Fig. 26–2).[1, 2, 8, 13–16] The tricuspid valve is occasionally infected, but pulmonic valve endocarditis is exceedingly rare. Fresh vegetations consist of three layers: (1) a large inner layer of platelets, fibrin, red and white blood cells, and some bacteria; (2) a middle layer of bacteria; and (3) an outer layer composed primarily of fibrin.[17] Most of the leukocytes within a vegetation are lymphocytes and histiocytes, and there are comparatively few polymorphonuclear cells. More mature vegetative lesions show evidence of capillary proliferation and fibroplasia. Mature vegetations are composed of dense, fibrous tissue and are covered by endothelium. Older vegetations are less friable than freshly formed ones and are often calcified.

PATHOGENESIS

BACTEREMIA

Transient or persistent bacteremia is an absolute requirement for the establishment of a cardiac infection. The initiating episode of bacteremia is not identified in most spontaneously occurring cases of IE.[18] When a predisposing event is identified, the conditions incriminated most often are medical and surgical procedures involving the oropharynx, gastrointestinal, and genitourinary tracts; dental manipulation; intravenous catheterization; pacemaker implantation; immunosuppressive drug therapy; and prior valvular infections.[8, 19–21]

Endocarditis occurring in association with dental procedures has received much attention. The incidence of bacteremia associated with dental procedures or tooth extraction has been reported to be as high as 85 percent, but few of these individuals develop endocarditis even when the duration of bacteremia is prolonged.[22] The likelihood and severity of bacteremia seem more related to the degree of periodontal disease than to the specific dental procedure.[22] Rocking of teeth, chewing hard candy, and even simple tooth brushing have been shown to cause transient bacteremia in people.[23] Other medical procedures causing transient bacteremia include bronchoscopy, the dilation of esophageal strictures, oral intubation, nasal operations, and transesophageal echocardiography.[24–28]

ESTABLISHMENT OF A CARDIAC INFECTION

The pathogenesis of infective endocarditis is complex, involving a number of factors relating to endothelial integrity, disturbed blood flow, bacterial virulence, and host immunity.[29–31] Healthy, intact endothelium is only weakly receptive to bacterial attachment.[32, 33] Damaged or denuded vascular endothelium readily promotes the development of platelet fibrin aggregates, and such lesions provide a susceptible nidus for bacterial invasion and colonization.[31] The term nonbacterial thrombotic endocarditis (NBTE) was coined by Zeiger in 1888 to describe the formation of sterile clumps of platelets, fibrin, and red cells on normal or superficially damaged cardiac valves.[34] An important predisposing cause of NBTE lesions is endothelial damage resulting from high-velocity, turbulent blood flow as occurs with pre-existing valvular insufficiency or stenosis. In-dwelling vascular catheters also induce local flow disturbances and directly damage vascular endothelium, promoting the formation of NBTE.[35] Hypercoagulable states, such as disseminated intravascular coagulation (DIC), also predispose patients to the formation of NBTE.[34]

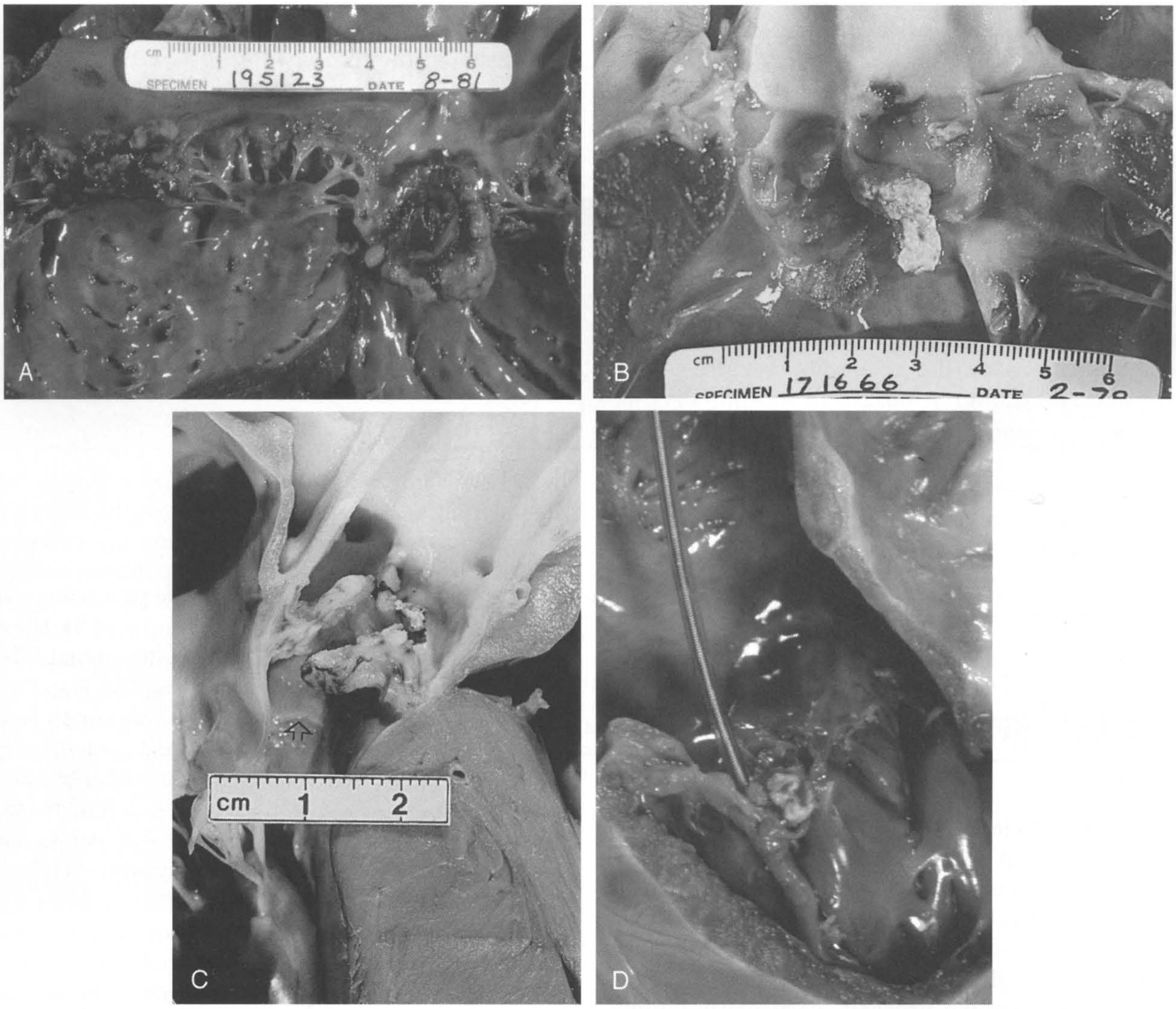


FIGURE 26–2

Bacterial endocarditis develops most often on the mitral (A) and aortic (B) valves of dogs and cats. (A) In this dog, proliferating vegetative lesions were identified on the anterior and posterior mitral valve leaflets. The anterior mitral valve leaflet is diffusely thickened and its surface is ulcerated and hemorrhagic. (B) Destruction of the right coronary cusp and avulsion of the noncoronary cusp of the aortic valve is shown in a dog with bacterial endocarditis. A contact lesion where the flail aortic leaflet impacted the ventricular septum is seen just below the valve.

In (C) and (D), two predisposing causes of infectious endocarditis are apparent. (C) Sagittal section through the left ventricular outflow tract and left ventricle of a dog with subaortic stenosis and infectious endocarditis of the aortic valve. Notice the proliferative endocarditis lesion involving all valve leaflets. The heterogeneous appearance of the aortic valve represents areas of fibrosis and dystrophic calcification. Destruction of the valve leaflets resulted in aortic insufficiency. Just below the aortic valve, a subtle white ring can be detected *(arrowhead)*. This is the pathologic lesion of mild subvalvular aortic stenosis. (D) In this specimen, a vegetation is seen on the tricuspid valve of a dog with a transvenous pacing lead positioned in the right ventricle. The animal was receiving immunosuppressive drugs for lymphosarcoma and had an indwelling venous catheter when it developed endocarditis.

A bacterium's ability to adhere to damaged endothelial surfaces plays a major role in determining its capacity to colonize a valve.[36] When the endothelium is damaged, organisms with well-developed mechanisms of adherence can overcome host defenses even at low levels of inoculation. Damage to endothelial surfaces exposes the extracellular polysaccharide dextran, which facilitates the attachment of some bacterial species.[35, 37] Valvular endothelium rich in fibronectin facilitates the binding of certain organisms, such as *Staphylococcus aureus*, that possess fibronectin receptors.[31] To sustain a cardiac infection, the invading pathogen must evade the host's defensive mechanisms. Very few granulocytes are observed in established vegetations, and the clusters of microorganisms therein are protected by layers of fibrin, platelets, and a few red

cells. The valves and the attached vegetation are also relatively avascular, limiting the access of antibodies, phagocytic cells, and antibiotics.[37–39]

DISTRIBUTION OF LESIONS

When high pressure drives an infected stream into a low pressure sink, a reproducible pattern of bacterial deposition occurs, as demonstrated in Rodbard's classic experiment.[40] This study explains the typical locations of IE lesions on the ventricular surface of the aortic valve and the atrial surface of the mitral valve. The location of endocarditis lesions in the pulmonary artery of patients with a patent ductus arteriosus, in the vein of an arteriovenous fistula, and distal to the narrow isthmus of a coarcted aorta is also consistent with the results of Rodbard's studies.[14, 40] The distribution of IE lesions within the heart can also be explained as a function of the pressure exerted on the valve.[41]

CARDIAC SEQUELAE

Valvular insufficiency is the most common cardiac sequela to bacterial endocarditis, developing as a consequence of valvular necrosis, perforation, or rupture of the chordae tendineae.[1–3, 8] The severity of valvular destruction varies with the virulence of the infecting organism and the duration of the infection. Destruction of the valve stroma proceeds particularly rapidly in acute, ulcerative endocarditis caused by *S. aureus*. Left-sided heart failure develops in most dogs developing aortic valve endocarditis and occurs commonly in dogs with mitral valve endocarditis.[2, 8, 13, 15] Obstruction of a valve orifice by large vegetations is uncommon. Extension of infection into the valve annulus, sinus of Valsalva, pericardium, or myocardium may result in abscess formation, aortoatrial shunting, purulent pericarditis, myocarditis, or destruction of the conduction system.[2, 42]

SYSTEMIC SEQUELAE

SYSTEMIC EMBOLIZATION AND METASTATIC INFECTION

Septic embolization and sterile arterial embolization, resulting in infarction and metastatic infection, are common in animals with bacterial endocarditis. The kidney and spleen are the most common sites of infarction at necropsy, but the heart, brain, intestine, and other large organs may be affected (Fig. 26–3).[2, 8] Death due to the combined effects of renal infarction, renal infection, and glomerulonephritis occurs in a substantial percentage of dogs with IE.[43, 44] On occasion, death results from myocardial infarction caused by embolic occlusion of a coronary artery.[45] Since infections in remote areas may be primary or secondary (metastatic), the pathogenesis of septic arthritis, urinary tract infections, or discospondylitis in animals with IE is often uncertain.[2, 8]

IMMUNE-MEDIATED DISORDERS

Stimulation of humoral and cellular immune systems by persistent bacteremia accounts for many extracardiac manifestations of IE.[39, 46] Rheumatoid factor, antinuclear antibodies, and circulating immune complexes contribute to the development of polyarthritis, renal disease, and myocarditis in dogs with IE.[47–49] Glomerulonephritis is a well-known complication of IE, and its prevalence and severity seem to vary in relation to the specific infecting organism.[50, 51] Glomerulonephritis may cause proteinuria, loss of antithrombin III, and a hypercoagulable state, thereby promoting the development of nonbacterial thromboembolism and new IE lesions.[52] A high correlation exists between the concentration of circulating immune complexes, the presence and severity of glomerulonephritis, and rheumatoid factor.[39]

Polyarthritis is particularly common and well documented in dogs with IE.[47, 48] Bacterial cultures of the joint fluid are often positive, but many affected dogs have negative cultures. Examination of the synovial tissues may be positive for IgG, IgM, and complement, indicating an immune-mediated basis for the arthropathy. Lameness in some dogs with IE has been attributed to the phenomenon of hypertrophic osteopathy.[2, 53] Such lesions are thought to be analogous to clubbing of the digits observed in some human patients with IE. A recent hypothesis suggests that platelet clumps shed from vegetative lesions are trapped in the microcirculation where they release platelet-derived growth factor, which acts as the stimulus for the hypertrophic osteopathy lesions.[54]

SEPSIS AND SEPTIC SHOCK

Animals with bacterial endocarditis are septic by definition—their disease is the result of pathogenic microorganisms and/or their toxins in the blood or tissues. Some animals with endocarditis will die of septic shock and multiple organ dysfunction, and it is helpful to be familiar with some of the terminology currently used in relation to patients with sepsis (chapter 15). *Sepsis syndrome* is the clinical state in which

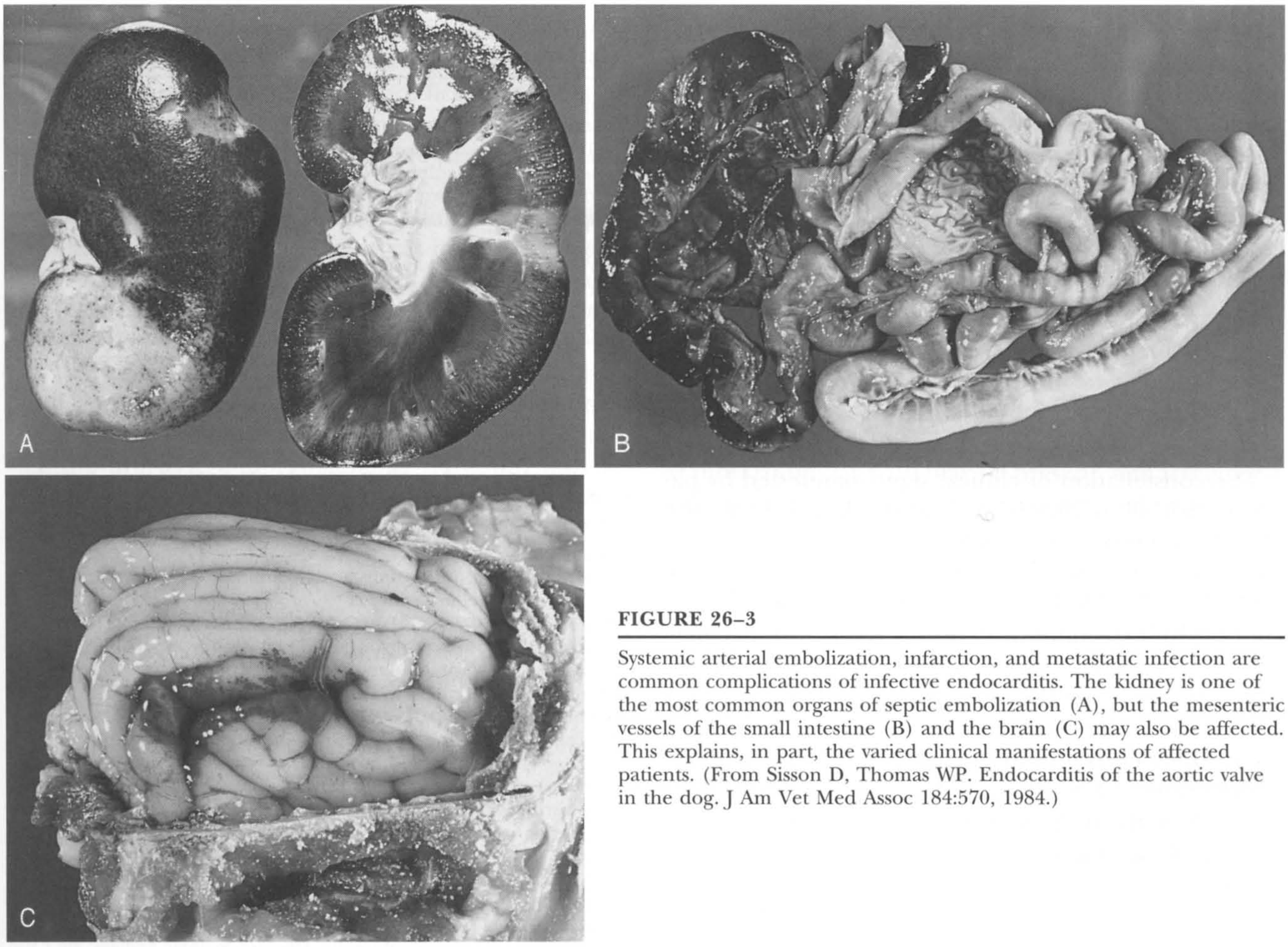


FIGURE 26–3

Systemic arterial embolization, infarction, and metastatic infection are common complications of infective endocarditis. The kidney is one of the most common organs of septic embolization (A), but the mesenteric vessels of the small intestine (B) and the brain (C) may also be affected. This explains, in part, the varied clinical manifestations of affected patients. (From Sisson D, Thomas WP. Endocarditis of the aortic valve in the dog. J Am Vet Med Assoc 184:570, 1984.)

there are obvious indications of altered organ perfusion, such as altered mentation, oliguria, acidosis, and/or hypoxemia. When hypotension complicates sepsis syndrome, the patient is experiencing *septic shock. Multiple organ dysfunction syndrome* (MODS) describes situations in which septic shock has progressed to cause any combination of DIC, acute respiratory distress, acute renal failure, hepatobiliary compromise, or central nervous system dysfunction. The progression to septic shock and MODS is thought to be prevented by appropriate therapy.

In animal models, the inflammatory cascade leading to sepsis and septic shock follows a predictable course.[55] The proinflammatory cytokines tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1) are released from macrophages and other inflammatory cells as a result of contact with bacterial endotoxin or other microbial components or products.[56–59] These compounds activate endothelial cells and other effector cells, such as T and B lymphocytes, monocytes, macrophages, and neutrophils, and they induce the release of other inflammatory cytokines, such as IL-8 and IL-6, transforming growth factor beta (TGF-β), prostaglandin E_2 (PGE_2), colony-stimulating factor, platelet-activating factor, eicosanoids, and other inflammatory mediators.[56–61] These compounds elicit a variety of physiologic effects that together constitute the phenomenon of sepsis. The intensity of the inflammatory response is controlled by regulatory mechanisms that include the acute-phase proteins, antiproteases, anti-inflammatory cytokines, and by specific anticytokine substances, including IL-1, various receptor antagonists, and the activity of soluble cytokine receptors.[56, 61]

In several animal models of endotoxemia or bacteremia, survival has improved when the actions of IL-1 are blocked by infusion of the naturally occurring IL-1 receptor antagonist (ILRA).[62] Preliminary reports evaluating ILRA in human patients with sepsis have mixed results.[63] Studies examining the inhibition of IL-1 and TNF-α release and other mediators are ongoing.

DIAGNOSIS

It is often difficult to establish a diagnosis of IE with certainty. Several studies have attempted to remedy this problem by defining reliable clinical criteria for establishing a diagnosis of IE.[64, 65] The most recently

formulated criteria emphasize the results of blood culture, visualization of vegetative lesions by echocardiography, clinical documentation of a new regurgitant murmur, and substantive clinical or laboratory indications of systemic embolization.[65] Applying this scheme retrospectively to patients with documented disease indicates that it offers superior sensitivity to previously used diagnostic criteria without compromising specificity.[64, 65] Slight modification of this scheme allows it to be applied to veterinary patients (Tables 26–1, 26–2).

HISTORY

The constellation of clinical signs manifested by patients with IE is diverse and misleading due to the high prevalence of embolic phenomena, metastatic infections, and immune-mediated sequelae. Thus, the problems identified by the owners of animals with endocarditis are quite varied and often nonspecific.[2, 66, 67] On occasion, an owner indicates the recent occurrence of some predisposing event, such as a dental procedure, upper respiratory or genitourinary surgery, intravenous catheterization, pacemaker implantation, immunosuppressive drug therapy, or prior infection. More often, the owners relate a vague history of generalized malaise, anorexia, and depression.

Many animals with IE eventually develop signs of congestive heart failure, such as cough, shortness of breath, weakness, or collapse.[2, 48, 66] Some patients present with a clinical history suggestive of systemic thromboembolism. Such signs include hematuria, lameness, seizures, or altered mentation, depending on the particular organ system(s) involved. Intermittent or persistent lameness is particularly common in dogs with endocarditis, causing confusion with a variety of orthopedic and musculoskeletal diseases.[2, 48, 68] The great diversity of clinical signs in patients with endocarditis has prompted some clinicians to refer to IE as the *great imitator.*

TABLE 26–1
Criteria for Diagnosis of Infective Endocarditis

Definite Infective Endocarditis
Pathologic Criteria
- Microorganisms demonstrated by culture or histology in a vegetation, *or*
- Microorganisms in a vegetation that has embolized, *or*
- Vegetation confirmed by histology showing active endocarditis

Clinical Criteria (Table 26–2)
- Two major criteria, *or*
- One major criteria and three minor criteria, *or*
- Five minor criteria

Possible Infective Endocarditis
Findings consistent with infective endocarditis but that fall short of "definite" though they are not in the "rejected" category

Rejected
- Firm alternative diagnosis *or*
- Resolution of clinical manifestations with antibiotic therapy for <4 days, *or*
- No pathologic evidence of infective endocarditis at surgery or autopsy after antibiotic therapy ≤4 days

Modified from Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of endocarditis: utilization of specific echocardiographic findings. Am J Med 96:200–209, 1994.

TABLE 26–2
Definitions of Major and Minor Criteria

Major Criteria
Positive blood culture for infective endocarditis
Typical microorganism for infective endocarditis from two separate blood cultures: *Corynebacterium* spp, *Erysipelothrix rhusiopathiae* (typically serovar 7), *Streptococcus* spp, *Staphylococcus* spp, *Pseudomonas aeruginosa, Pasteurella* spp in the absence of a primary focus, *or*
Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis form:
(1) Blood cultures drawn more than 12 hours apart, *or*
(2) All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hour apart
Evidence of endocardial involvement
Positive echocardiogram for infective endocarditis
Oscillating intracardiac mass on valve or supporting structures, *or* in the path of regurgitant jets, *or* on implanted material, in the absence of an alternative anatomic explanation, *or* abscess
New valvular regurgitation* (increase or change in preexisting regurgitation not sufficient)

Minor Criteria
Predisposition: predisposing heart condition (subaortic stenosis), chronic indwelling catheter
Fever†
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, intracranial hemorrhage, conjunctival hemorrhages
Immunologic phenomena: glomerulonephritis, vasculitis, polyarthropathy (+/− rheumatoid factor)
Microbiologic evidence: positive blood culture but not meeting major criteria as noted previously *or* serologic evidence of active infection with organism consistent with infective endocarditis
Echocardiogram: consistent with infective endocarditis but not meeting major criteria as noted previously

*Requires recent prior auscultation.
†At presentation or historically documented.
Modified from Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of endocarditis: utilization of specific echocardiographic findings. Am J Med 96:200–209, 1994.

PHYSICAL EXAMINATION

FEVER

Most dogs with IE have pyrexia at presentation, or a history of recurrent febrile episodes.[2, 3, 13–15] Some notable exceptions include those animals receiving antibiotics, aspirin, or corticosteroids, and those with chronic infections, renal failure, or heart failure.[2, 13, 42, 69] The presence of a fever is very helpful in establishing a diagnosis of IE when it is detected in association with other clinical findings.

HEART MURMURS

The development of a new or changing cardiac murmur is another hallmark of valvular endocarditis. Doc-

umentation of a new murmur is often difficult as one must verify that it was not present on a recently conducted prior examination.[66] The predictive value of a recently discovered heart murmur is most dependent on its character and location, as these parameters suggest which valve is affected and the severity of the abnormality. Detection of a diastolic murmur at the left heart base in a febrile dog or cat indicates a high probability of aortic valve endocarditis simply because other causes of aortic insufficiency are rare.[2, 8] By comparison, a systolic murmur in a febrile, small-breed dog has little predictive value because degenerative mitral valve disease is very prevalent in this population (chapter 25). In most animals with mitral regurgitation, the murmur is holosystolic in duration, with a harsh, mixed-frequency quality. Loud systolic murmurs of aortic stenosis or mitral regurgitation often mask the softer, lower-frequency murmur of aortic regurgitation.

The importance of a rapidly changing murmur as an indicator of IE has been overemphasized.[8] Physiologic murmurs and mitral regurgitant murmurs are often variable in duration and intensity due to changes in stroke volume, preload, and afterload. Nonetheless, serial examinations documenting alterations in the character of the murmur can provide important prognostic information. For example, the murmur of mild aortic insufficiency is typically holodiastolic, and its intensity diminishes only slightly over the entire diastolic interval. When aortic insufficiency becomes more severe, the intensity of the diastolic murmur diminishes throughout diastole, and it may not be audible in the latter part of diastole. This finding indicates equilibration of aortic and left ventricular diastolic pressures caused by the volume overload imposed by aortic regurgitation, and it suggests impending heart failure.

MYOCARDITIS AND HEART FAILURE

A variety of rhythm disorders may be detected in dogs with IE as a consequence of myocarditis, heart failure, myocardial infarction, or destruction of the conduction system.[2, 13, 14] Ventricular arrhythmias are particularly common in animals with IE. Damage to the atrioventricular node or the bundle of His may result in heart block and symptomatic bradycardia. A third heart sound (S_3 gallop) is often detected in dogs or cats with severe aortic or mitral regurgitation. Cough, tachypnea, labored respiration, and abnormal lung sounds may also be detected when heart failure develops. With developing aortic regurgitation, the femoral pulses become exaggerated or bounding. Small amplitude, weak arterial pulses are palpated in animals with pre-existing subvalvular aortic stenosis, following the onset of heart failure, and in the rare circumstance of acquired aortic stenosis caused by a large vegetative lesion on the aortic valve. Unequal or absent femoral artery pulses suggest arterial thromboembolism. Irregular pulses and pulse deficits are usually associated with conduction or rhythm disturbances, indicating the need to obtain an electrocardiogram.

SYSTEMIC ABNORMALITIES

The physical manifestations of peripheral embolization, metastatic infection, and immune-mediated phenomena are diverse. Vasculitis, arthralgia, and joint effusions resulting from immune-mediated or septic arthritis are common in animals with IE. Abdominal or thoracolumbar pain may be present, and irregularly shaped kidneys or abdominal masses (splenomegaly) may be palpable. A variety of neurologic deficits may develop, most of which are of sudden onset, suggesting an embolic event. Retinal hemorrhages, hyphema, epistaxis, and petechiation of the skin or mucous membranes are occasionally noted. Myalgia and long-bone pain caused by emboli or hypertrophic osteopathy are infrequently detected. Most of the peripheral stigmata of IE observed in human patients (subungual splinter hemorrhages, Osler's nodes, Janeway's lesions, Roth's spots) are absent or go undetected in dogs and cats with IE.[8]

ECHOCARDIOGRAPHY

VISUALIZATION OF DEVELOPING VEGETATIONS

Echocardiography plays a pivotal role in the diagnosis and management of endocarditis.[2, 3, 49, 64, 65, 69–71] Two-dimensional echocardiography is used to visualize the primary lesion of infectious endocarditis (i.e., the developing vegetation), and to assess the consequences of that infection (e.g., dissolution or avulsion of a valve leaflet, chamber dilation and myocardial failure, abscess formation, and other complications). Because the aortic and mitral valves are the most commonly infected valves in dogs and cats, both valves should be evaluated with particular care. The early echocardiographic features of endocarditis often include only slight thickening or increased echogenicity of the affected valve. At this stage, hemodynamic changes are absent or minimal. As the disease progresses, the developing vegetation appears as an irregular area of highly reflective leaflet thickening or as a pedunculated mass, usually arising from the tip of the leaflet (Figs. 26–4, 26–5). In the majority of cases, the infected valve becomes insufficient when the valve stroma is destroyed, or when the vegetation prevents normal coaptation of the valve leaflets.[2, 49, 66] On rare occasion, a large, proliferating vegetative mass will obstruct a valve orifice, causing functional stenosis.

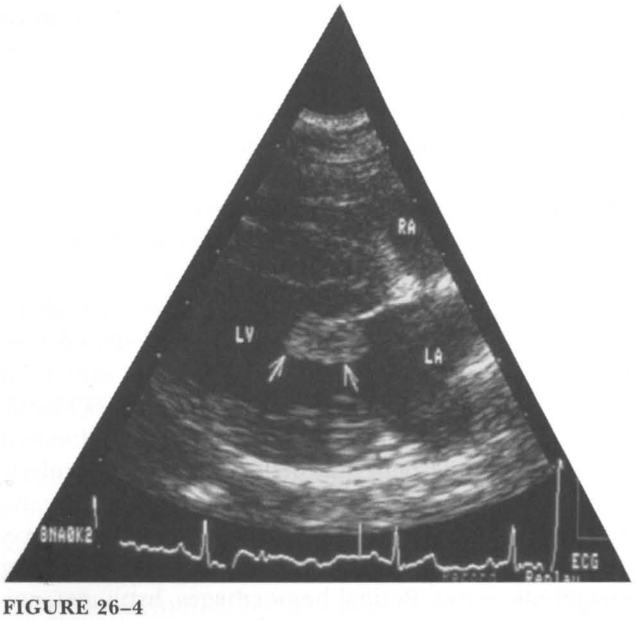


FIGURE 26–4

A large vegetative lesion *(arrows)* on the anterior mitral valve leaflet of a dog is shown in this right parasternal, four-chamber, long-axis echocardiogram. This dog subsequently suffered an infarction of the small intestine. RA, right atrium; LA, left atrium; LV, left ventricle.

Certain limitations of transthoracic echocardiography must be recognized. Small vegetations are very difficult to visualize, particularly in very small or obese patients. Tachypnea, dyspnea, or tachycardia may also preclude an optimal echocardiographic evaluation. In these circumstances, a diagnosis of infective endocarditis should not be ruled out based on a negative echocardiographic evaluation. However, the negative predictive value of a high-quality normal echocardiogram most likely exceeds 90 percent in patients with no detectable cardiac murmur. Serial echocardiographic evaluations of patients suspect for IE can be particularly helpful because subtle alterations in valvular or mural endocardial echogenicity are more likely to be appreciated. Such changes may be the initial clinical finding supporting a diagnosis of IE. Transesophageal echocardiography (TEE) is more sensitive than transthoracic echocardiography for recognizing small vegetative lesions.[69–73] However, it is uncommonly used to image dogs and cats suspected of having endocarditis, particularly when they are seriously ill, because of the requirement for general anesthesia.

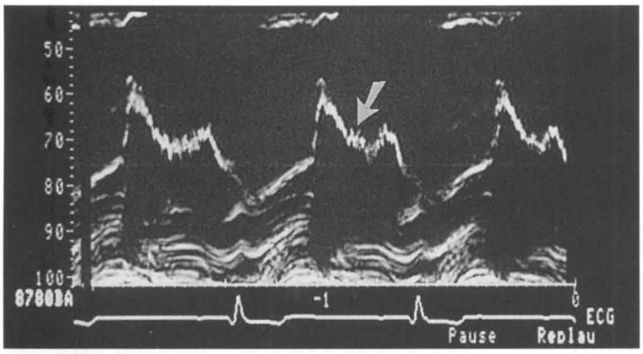


FIGURE 26–5

M-mode echocardiogram of the mitral valve from a dog with infectious endocarditis of the aortic valve and resultant aortic insufficiency. Notice the high-frequency vibrations of the anterior mitral valve during diastole *(arrow)*. This is caused by the jet of aortic regurgitation striking this valve when it opens in diastole.

M-MODE ECHOCARDIOGRAPHY

Certain subtle alterations in valvular motion are best appreciated using M-mode echocardiography, but this modality plays a relatively minor role in the echocardiographic evaluation of patients with or suspected of having endocarditis. High-frequency diastolic fluttering of the mitral valve, which is highly suggestive of aortic insufficiency, may not be apparent on two-dimensional studies but is easily seen on an M-mode echocardiogram (Fig. 26–5).[2, 74] The explanation for this phenomenon is quite simple. During diastole, the mitral valve is open and the anterior leaflet is situated immediately below the aortic valve in the left ventricular outflow tract. When a jet of aortic regurgitation is directed at the anterior mitral leaflet, it strikes the leaflet, causing high-frequency vibrations that are readily displayed on an M-mode echocardiogram.[2, 74] Other M-mode echo changes, such as premature closure of the mitral valve, may be observed when evaluating dogs with severe aortic insufficiency. When aortic regurgitation is severe, left ventricular pressure rises rapidly during diastole as blood flows retrograde from the aorta. If left ventricular pressure exceeds left atrial pressure, the mitral valve will close prematurely—prior to the onset of systole, at the peak of the R wave.[2, 74]

FLOW DISTURBANCES AND FUNCTIONAL CHANGES

The hemodynamic consequences of endocarditis are most dramatically illustrated by color flow Doppler imaging.[75] With this technique, blood flow disturbances can be quickly located and assessed. Precise quantification of valvular regurgitation is difficult. Techniques such as measuring decay rate, proximal jet area, and proximal jet height allow reasonable estimation of volumetric regurgitation.[75] The severity of volumetric regurgitation also may be reasonably inferred by the degree of left ventricular and left atrial dilation.

Echocardiography often yields other important information of prognostic value.[71, 76] For example, patients with a vegetation diameter of greater than 10

mm are at significantly higher risk for embolic phenomena than those with smaller vegetations.[1, 76] Evidence of left ventricular dysfunction, such as reduced fractional shortening percent, ejection fraction, and aortic flow acceleration, also suggests a poor long-term prognosis.[77] Regional wall motion abnormalities, especially when coupled with ventricular arrhythmia, can indicate septic embolization of a coronary artery.[78, 79] If the region of LV dysfunction is small, parameters of global wall function may remain within normal limits, giving an erroneous portrayal of normal LV function.[80]

BLOOD CULTURE

Multiple sets of blood cultures should be obtained whenever bacterial endocarditis is suspected. The sensitivity of blood cultures in human patients with endocarditis varies from 80 percent when a single culture is obtained up to 100 percent when three or more cultures are procured.[2, 66, 81–84] Positive blood cultures have been reported in about 75 percent of dogs with bacterial endocarditis.[8, 42] Increased sample volume substantially improves the sensitivity of blood culturing.[85] In one study, yields from cultures of 20 and 30 ml of blood were shown to be 38 percent and 62 percent higher, respectively, than from 10 ml of blood.[86] Volumes of blood larger than this do not increase yield but increase the likelihood of iatrogenic anemia. It is important not to place larger volumes of blood into media bottles designed for 10-ml blood samples. The blood in blood culture vials is diluted at 1:5 to 1:10 to reduce the concentration of circulating antibacterial factors (complement, immunoglobulins, phagocytes). The possibility of accidental contamination is less likely when the same organism is cultured from several different blood samples. In this regard, each culture should be obtained from a different venipuncture site. Regardless of the volume of blood obtained or number of bottles inoculated, blood obtained from a single venipuncture constitutes one culture.

Other recommendations for blood culture techniques are changing as some widely held beliefs regarding blood cultures are being re-evaluated.[81, 86–89] Over the last few decades, the number of anaerobic isolates from blood cultures obtained from human patients with IE has diminished greatly.[1, 83] Such studies have prompted some to recommend only aerobic blood culturing.[87] With these considerations in mind, two alternative culturing techniques can be considered: (1) Each 20-ml sample of blood can be divided and inoculated into aerobic and anaerobic media, or (2) 20 ml of blood can be used to isolate aerobic species only. The latter method emphasizes the importance of blood volume on culture yields and assumes that there is a low likelihood of a positive anaerobe culture. The relative merits of these two approaches in veterinary patients is uncertain.

Bacteremia is known to precede the development of a recurring fever by 1 or 2 hours.[89] This fact is of limited clinical utility because it is virtually impossible to predict when a fever spike will occur in patients with intermittent bacteremia. In these circumstances, the infecting organism is most likely to be cultured and identified when multiple sets of blood cultures are collected at wide intervals. The timing of blood culturing is irrelevant in those clinical situations in which continuous bacteremia is suspected, such as patients with endocarditis and septic thrombophlebitis. In patients receiving antibiotics, blood culture collection should be accomplished during the trough levels of antibiotics.[90–92] The belief that blood cultures should not be obtained from an indwelling catheter has recently been challenged.[88] When the blood culture results of samples drawn through indwelling intravenous and arterial cannulas were compared with samples drawn simultaneously by percutaneous venipuncture, 92 percent of 174 comparisons were identical.[89] This study, performed in humans, has not yet been duplicated in dogs and cats.

ELECTROCARDIOGRAPHY AND THORACIC RADIOGRAPHY

Electrocardiography detects arrhythmia and conduction disturbances in as many as 50 to 75 percent of the dogs with IE.[2, 49, 66] Reported rhythm disorders include atrial and ventricular premature depolarizations, paroxysmal and sustained tachyarrhythmia, bundle branch block, and first-, second-, and third-degree atrioventricular block.[2, 13, 49] Arrhythmias develop as a consequence of bacterial invasion into the myocardium, from myocardial hypoxia, from embolism of portions of vegetations into the coronary circulation, and as a result of immune-mediated vasculitis. Serious arrhythmias, such as sustained ventricular tachycardia and atrial fibrillation, negatively affect prognosis.[2]

Thoracic radiography is most useful for evaluation of the pleural space and pulmonary parenchyma and specifically for the detection of left-sided congestive heart failure. Radiographically detectable left atrial and ventricular enlargements are observed only when moderate-to-severe valvular insufficiency has developed. Serial radiographic evaluation is particularly helpful for assessing those patients with rapidly progressing valvular insufficiency. As a general rule, echocardiography is more sensitive and more specific than radiography or electrocardiography for detecting cardiac chamber enlargement.

THERAPY

Antimicrobial therapy is the mainstay of treatment for patients with IE, but such therapy must often be combined with other medicaments or interventions. The goals of therapy are (1) to sterilize the vegetative lesion(s), (2) to attend to any adverse cardiac sequelae, and (3) to manage any systemic abnormalities associated with the infection.

ANTIBIOTIC REGIMENS

Bactericidal antibiotics capable of penetrating the fibrin-rich matrix of vegetations should be administered for at least 2 weeks and for as long as 6 weeks to ensure complete kill of the offending organism. Intravenous administration of bactericidal antibiotics is advisable initially to ensure that minimum bactericidal concentrations are rapidly attained.[2, 8, 66] Although antibiotic regimens ideally are selected based on culture and sensitivity testing, therapy is usually instituted before culture results are known. Considering the wide range of microorganisms isolated from dogs and cats with endocarditis, initial treatment with gentamicin or amikacin in combination with penicillin, ampicillin, oxacillin, or nafcillin is reasonable.[2, 8, 93–95] More complete anaerobic coverage can be realized by the addition of clindamycin or metronidazole. This treatment regimen is also appropriate in IE cases with negative blood culture results.

Knowledge of those organisms commonly isolated from animals with IE and sepsis, and the typical susceptibility patterns of those organisms, helps guide therapy (Tables 26–3, 26–4). Specific regimens for treating IE in humans have been developed and should be consulted when uncommon or highly resistant organisms are cultured in a dog or cat. The toxicity of the aminoglycosides usually limits their use to the initial 5 to 7 days of treatment. Thereafter, antimicrobials suitable for prolonged administration must be selected. There is increasing interest in the fluoroquinolones and third-generation cephalosporins for treating difficult infections.[96, 97] The efficacy of the fluoroquinolones for treating bacterial endocarditis is uncertain, and the emergence of resistant organisms is of growing concern with this group of antimicrobials.[96] The third-generation cephalosporins (cefotaxime, moxalactam, cefoperazone, ceftizoxime) have gram-positive, gram-negative, and anaerobic spectra and are highly β-lactamase resistant. Imipenem, a carbapenem antibacterial agent, has the widest spectrum of any β-lactam antibiotic. It is resistant to type I β-lactamase and is an attractive choice as empiric therapy for patients with sepsis.[97] In patients with compromised renal function, a first-generation cephalosporin (cephalothin, cefazolin, cephalexin, cefadroxil) is likely to be efficacious for gram-positive infections but has only intermediate efficacy against gram-negative infections or anaerobes. When gram-negative or anaerobic infection is suspected, a second-generation cephalosporin (cefoxitin, cefamandole, cefotetan, cefaclor, cefonicid) would be more advisable.

TABLE 26–3
Organisms Commonly Recovered from Dogs and Cats with Infective Endocarditis and Sepsis

Infectious Endocarditis	
Corynebacterium spp (typically serovar 7)	
Streptococcus spp	
Staphylococcus spp	
Pseudomonas aeruginosa	
Escherichia coli	
Erysipelothrix rhusiopathiae	
Sepsis/Bacteremia	
Proteus	*Bacteroides**
*Salmonella**	*Enterococcus*
Corynebacterium spp	*Erysipelothrix rhusiopathiae*
Streptococcus spp	*Staphylococcus* spp
Pseudomonas aeruginosa	*Escherichia coli**
*Klebsiella pneumoniae**	*Clostridium**
Fusobacterium	

*Common isolates from bacteremic cats.

HEART FAILURE AND ARRHYTHMIA

Heart failure is the most common cause of death in dogs with infectious endocarditis.[2, 8] Because valve replacement surgery is unavailable to most veterinary patients, the development of serious valvular insufficiency or heart failure warrants a poor or grave prognosis, particularly in dogs with aortic endocarditis.[2] Signs of heart failure may be palliated by administration of cardiac glycosides, diuretics, and a vasodilator or angiotensin-converting enzyme inhibitor. Compared with digitalis alone, vasodilators decrease the progression of myocardial hypertrophy and lessen the severity of myocardial dysfunction.[98, 99] Blood pressure should be carefully monitored in patients with aortic regurgitation as they frequently have low diastolic pressure and are at increased risk for hypotension. Placement of a synthetic valvular prosthesis or allograft is a possible treatment option, but this remedy has not been reported in dogs or cats with endocarditis.[100–102]

Life-threatening arrhythmia or those rhythm disorders with serious hemodynamic consequences should be treated with appropriate antiarrhythmic drugs (chapters 17, 18). High-grade second-degree or complete atrioventricular block may necessitate pacemaker implantation. This causes a formidable dilemma in that infection of the implanted device is likely, posing another potentially devastating complication.[103]

TABLE 26-4
Antibiotics Commonly Used in the Therapy of Infectious Endocarditis and Sepsis

Classification	Representative Drugs/ Dose/Route	Spectrum	Comments
Aminoglycosides	Gentamicin, 2–4 mg/kg q8h IV Amikacin, 7–10 mg/kg q8h IV	Gram −, *Staph aureus*	Ototoxicity, nephrotoxicity, therapeutic serum levels: Gentamicin: trough (should drop below) 2 μg/ml, peak (should not exceed) 8–12 μg/ml. Amikacin: trough 2.5 μg/ml, peak 25 μg/ml
Carbapenem*	Imipenem, 2–5 mg/kg q8h IV	Gram +, gram −, anaerobes	Resistant to type I ß-lactamase; decrease dose with renal dysfunction; may cause GI upset and hypersensitivity
1st-generation cephalosporins	Cefazolin, 15–33 mg/kg q8h IV, IM Cephalexin, 20–60 mg/kg q8h PO	Gram +, intermediate against gram −	Ineffective against anaerobic spp, especially *Bacteroides fragilis* and *Bacteroides* spp
2nd-generation cephalosporins	Cefoxitin 25–40 mg/kg q8h IV, IM Cefaclor 6–13 mg/kg q8h PO	Gram +, anaerobes, gram − (not *Pseudomonas* spp)	Cephalosporins may cross-react in penicillin-sensitive people and are ineffective against *Clostridium* spp
3rd-generation cephalosporins*	Cefotaxime, 20–80 mg/kg q8h IV Moxalactam, 50 mg/kg IV, IM q6–8h	Gram +, gram −, anaerobes	Highly ß-lactamase resistant; may impair coagulation and platelet function; cross-react in penicillin-sensitive people
Lincosamide	Clindamycin, 5–15 mg/kg q1h IV; 22 mg/kg q24h PO	*Strep* spp, *Staph* spp, anaerobes (especially *Bacteroides* spp)	Good leukocyte and tissue penetration; IV fusion may cause hypotension; do not use with chloramphenicol
Nitroimidazole	Metronidazole, 10–15 mg/kg q8h IV, PO	Protozoa, obligate anaerobes, **not** facultative anaerobes or obligate aerobes	Good tissue penetration; may cause GI (nausea, vomiting) and CNS (ataxia, nystagmus, seizures) signs
Penicillins	Ampicillin, 20–50 mg/kg q8h IV, IM, PO Amoxicillin, 20–30 mg/kg q8h IV, IM, PO	Gram + (*Strep* spp, some *Staph* spp), anaerobes (**not** ß-lactamase producers)	Have been associated with hypersensitivity in some people
ß-Lactamase–resistant penicillins	Nafcillin, 25–50 mg/kg q6h IV amoxicillin/clavulanate, 11–22 mg/kg q8h PO	Gram + (most *Staph* spp), **not** anaerobes or gram − organisms	May cross-react in penicillin-sensitive people
Carboxypenicillins	Ticarcillin, 40–75 mg/kg q6–8h IV, IM Carbenicillin, 20–40 mg/kg q4–8h IV, IM	Gram + (most *Staph* spp), gram − and anaerobes	May prolong bleeding time and reduce platelet function
Quinolones	Enrofloxacin, 5 mg/kg q12h, PO, IM, IV Norfloxacin, 22 mg/kg q12h PO	Gram − and *Staph aureus*, **not** *Strep* spp	May be effective if bacterial resistance to aminoglycosides has developed

*Represents antibiotic groups that would be appropriate single-agent therapy in infections of unknown, potentially mixed origin.

SYSTEMIC INFECTIONS AND SEPSIS

Patients with septic shock are particularly difficult to treat, and the best approach to such patients is uncertain. Although high doses of glucocorticoids given prior to or within the first 2 hours of the onset of sepsis improve survival in experimental models of septic shock, their use has an adverse effect on the survival of dogs with infective endocarditis.[2, 49, 66, 104–106] Manipulation of the individual mediators of sepsis, although replete with potential benefit, has been met with ambiguous clinical results.[107, 108] The treatment for sepsis includes antibiotic therapy and supportive care (chapters 14, 15).

PREVENTION

The prophylactic use of antibiotics for this condition is controversial.[2, 39, 109–112] Citing the severe consequences of infective endocarditis, most authoritative sources urge antibiotic treatment of patients with predisposing cardiac conditions when they are subjected to procedures causing bacteremia.[18, 110] The authors recommend IE prophylaxis in dogs with predisposing cardiovascular lesions (subaortic stenosis, ventricular septal defect, patent ductus arteriosus, cyanotic congenital heart disease) undergoing dental scaling, tooth extraction, and surgery of the upper respiratory, gas-

trointestinal, or infected genitourinary tracts. The antibiotic selected depends upon the nature of the procedure and the organism most likely to cause bacteremia. Accordingly, amoxicillin, administered orally, or ampicillin IM or IV 1 hour before and 6 hours after the initial dose, is recommended for use with dental, oral, and upper respiratory tract procedures. Ampicillin and gentamicin, administered IV 30 minutes before the procedure and 8 hours after the initial dose, is recommended for use with genitourinary or gastrointestinal procedures.[110]

A growing number of investigators have challenged the administration of antibiotics to prevent endocarditis. It has been argued that only 6 percent of all human cases of IE could be prevented with prophylaxis.[5, 113] Given the expense and possible adverse effects of antibiotics, the risk-to-benefit ratio and economic rationale of prophylactic antibiotic treatment have also been questioned. Despite these concerns, prophylaxis against IE is practiced in most developed countries.

REFERENCES

1. Shouse CL, Meier H. Acute vegetative endocarditis in the dog and cat. J Am Vet Med Assoc 129:278, 1956
2. Sisson D, Thomas WP. Endocarditis of the aortic valve in the dog. J Am Vet Med Assoc 184:570, 1984
3. Lombard CW, Buergelt CD. Vegetative bacterial endocarditis in dogs; echocardiographic diagnosis and clinical signs. J Small Anim Pract 24:325, 1993
4. Buchanan JW. Causes and prevalence of cardiovascular disease. *In* Kirk RW, Bonagura JD (eds). Current Veterinary Therapy 11: Small Animal Practice. Philadelphia, WB Saunders, 1992, p 647
5. Malik R, Church DB, Allan GS, et al. What is your diagnosis? J Am Vet Med Assoc 200:1391, 1992
6. Noakes ME. What is your diagnosis? J Am Vet Med Assoc 193:719, 1988
7. Yamaguchi RA, Pipers FS, Gamble DA. Echocardiographic evaluation of a cat with bacterial vegetative endocarditis. J Am Vet Med Assoc 183:118, 1983
8. Sisson DD. Bacterial Endocarditis. Proceedings, 18th Annual Kal Kan/OSU Symposium, 1994, p 79
9. Fowler VG, Durack DT. Infective endocarditis. Curr Opinion Cardiol 9:389, 1994
10. Steckelberg JM, Wilson WR. Risk factors for infective endocarditis. Infect Dis Clin North Am 7(1):9, 1993
11. Durack DT. Infective and noninfective endocarditis. *In* Hurst JW (ed): The Heart: Arteries and Veins. Vol 7. New York, McGraw-Hill, 1990, p 1230
12. Muna WF, Ferrans VJ, Pierce JE, et al. Discrete subaortic stenosis in Newfoundland dogs: association of infective endocarditis. Am J Cardiol 41:740, 1978
13. Calvert CA, Greene CE, Hardie EM. Cardiovascular infections in dogs: epizootiology, clinical manifestations, and prognosis. J Am Vet Med Assoc 187:612, 1985
14. Goodwin JK, Lombard CW. Patent ductus arteriosus in adult dogs: clinical features of 14 cases. J Am Anim Hosp Assoc 28:349, 1992
15. Lundh T. Fibrinous endocarditis in dogs. Acta Vet Scand 5:17, 1964
16. Anderson CA, Dubielzig RR. Vegetative endocarditis in dogs. J Am Anim Hosp Assoc 20:149, 1984
17. Buchbinder NA, Roberts WC. Left-sided valvular infective endocarditis—a study of 43 necropsy patients. Am J Med 53:20, 1972
18. Durack DT. Prevention of infective endocarditis. N Engl J Med 332:38, 1995
19. Bender IB, Barkan MJ, Einstein A. Dental bacteremia and its relationship to bacterial endocarditis: preventive measures. Compend Contin Educ Dent 10:472, 1994
20. Everett ED, Hirschmann JV. Transient bacteremia and endocarditis prophylaxis; a review. Medicine 56:61, 1977
21. Weiss H. Relation of portals of entry to subacute bacterial endocarditis. Arch Intern Med 54:710, 1934
22. Black AP, Crichlow AM, Saunders JR. Bacteremia during ultrasonic teeth cleaning and extraction in the dog. J Am Anim Hosp Assoc 16:611, 1980
23. Wahl MJ. Myths of dental-induced endocarditis. Arch Intern Med 154:137, 1994
24. Terpenning MS, Buggy BP, Kauffman CA. Hospital-acquired infective endocarditis. Arch Intern Med 148:1601, 1988
25. Friedland G, Von Reyn CF, Levy B, et al. Nosocomial endocarditis. Infect Control 5:284, 1984
26. Sipes JN, Thompson RL, Hook EW. Prophylaxis of infective endocarditis: a reevaluation. Annu Rev Med 28:371, 1977
27. LeFrock JL, Ellis CA, Turchik JB, et al. Transient bacteremia associated with sigmoidoscopy. N Engl J Med 289:467, 1973
28. Pongratz G, Henneke K, von der Grun M, et al. Risk of endocarditis in transesophageal echocardiography. Am Heart J 125:190, 1993
29. Blahd M, Frank I, Saphir O. Experimental endocarditis in dogs. Arch Pathol 27:424, 1939
30. Freedman LR. The pathogenesis of infective endocarditis. J Antimicrob Chemother 20:1, 1987
31. Livornese LL, Korzeniowski OM. Infective Endocarditis. 2nd ed. New York, Raven Press, 1992, p 19
32. Durack DT, Beeson PB, Petersdorf RG. Experimental bacterial endocarditis. III. Production and progress of the disease in rabbits. Br J Exp Pathol 54:142, 1973
33. Ferguson DJ, McColm AA, Ryan DM, et al. A morphological study of experimental staphylococcal endocarditis and aortitis. II. Inter-relationship of bacteria, vegetation and cardiovasculature in established infections. Br J Exp Pathol 67:679, 1986
34. Lopez JA, Ross RS, Fishbein MC, et al. Nonbacterial thrombotic endocarditis: a review. Am Heart J 113:773, 1987
35. Baddour LM, Christensen GD, Lowrnace JH, et al. Pathogenesis of experimental endocarditis. Rev Infect Dis 11:452, 1989
36. Scheld WM, Valone JA, Sande MA. Bacterial adherence in the pathogenesis of endocarditis. J Clin Invest 61:1394, 1978
37. Johnson CM. Adherence events in the pathogenesis of infective endocarditis. *In* Wilson WR, Steckelberg JM (eds): Infect Dis Clin North Am, 1993, p 21
38. Durack DT. Experimental bacterial endocarditis. IV. Structure and evolution of very early lesions. J Pathol 115:81, 1975
39. Bayer AS, Theofilopoulos AN. Immunopathogenetic aspects of infective endocarditis. Chest 97:204, 1990
40. Rodbard S. Blood velocity and endocarditis. Circulation 27:18, 1963
41. Lepeschkin E. On the relation between the site of

valvular involvement in endocarditis and the blood pressure resting on the valve. Am J Med Sci 224:318, 1952
42. Woodfield JA, Sisson D. Infective endocarditis. *In* Ettinger SJ (ed): Textbook of Small Animal Internal Medicine. 3rd ed. Philadelphia, WB Saunders, 1989, p 1151
43. Taboada J, Palmer GH. Renal failure associated with bacterial endocarditis in the dog. J Am Anim Hosp Assoc 25:243, 1989
44. Cook HT, Macdougall DF, Steward AP, et al. Prospective survey of canine chronic renal disease and prevalence and types of canine glomerulonephritis. Abstract. J Pathol 146:276A, 1985
45. Swanwick RA, Williams OJ. Fatal myocardial infarct in a Greyhound. J Small Anim Pract 23:451, 1982
46. Phair JP, Clarke J. Immunology of infective endocarditis. Prog Cardiovasc Dis 22:137, 1979
47. Bennett D, Gilbertson EM, Grennan D. Bacterial endocarditis with polyarthritis in two dogs associated with circulating autoantibodies. J Small Anim Pract 19:185, 1978
48. Bennett D, Taylor DJ. Bacterial endocarditis and inflammatory joint disease in the dog. J Small Anim Pract 29:347, 1988
49. Elwood CM, Cobb MA, Stepien RL. Clinical and echocardiographic findings in 10 dogs with vegetative bacterial endocarditis. J Small Anim Pract 34:420, 1993
50. Neugarten J, Gallo GR, Baldwin DS. Glomerulonephritis in bacterial endocarditis. Am J Kidney Dis 3:371, 1984
51. Perez GO, Rothfield N, Williams RC. Immune-complex nephritis in bacterial endocarditis. Arch Intern Med 136:334, 1976
52. Green RA, Russo EA, Greene RT, et al. Hypoalbuminemia-related platelet hypersensitivity in two dogs with nephrotic syndrome. J Am Vet Med Assoc 186:485, 1985
53. Vulgamott JC, Clark RG. Arterial hypertension and hypertrophic pulmonary osteopathy associated with aortic valvular endocarditis in a dog. J Am Vet Med Assoc 177:243, 1980
54. Dickinson CJ. The aetiology of clubbing and hypertrophic osteoarthropathy. Eur J Clin Invest 23:330, 1993
55. Barron RL. Pathophysiology of septic shock and implications for therapy. Clin Pharm 12:829, 1993
56. Glauser MP, Heumann D, Baumgartner JD, et al. Pathogenesis and potential strategies for prevention and treatment of septic shock: an update. Clin Infect Dis 18(Suppl 2):S205, 1994
57. Henry WL, DeMaria A, Gramiak R, et al. Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-dimensional Echocardiography. Circulation 62:212, 1980
58. Mammen EF. Perspectives for the future (pathophysiology of sepsis). Intensive Care Med 19:S29, 1993
59. Calandra T, Baumgartner JD, Grau GE, et al. Prognostic values of tumor necrosis/cachectin, interleukin-1, interferon-alpha, and interferon-gamma in the serum of patients with septic shock. J Infect Dis 161:982, 1990
60. Fisher CJ, Opal SM, Dhainaut JF, et al. Influence of an anti-tumor necrosis factor monoclonal antibody on cytokine levels in patients with sepsis. Crit Care Med 21:318, 1993
61. Suffredini AF, Eichacker PQ, Danner RL, et al. Selected treatment strategies for septic shock based on proposed mechanisms of pathogenesis. Ann Intern Med 120:771, 1994
62. Suffredini AF. Current prospects for the treatment of clinical sepsis. Crit Care Med 22:S12, 1994
63. Knaus WA, Harrell FE, Fisher CJ, et al. The clinical evaluation of new drugs for sepsis: a prospective study design based on survival analysis. J Am Med Assoc 270:1233, 1993
64. Von Reyn CF, Levy BS, Arbeit RD, et al. Infective endocarditis: an analysis based on strict case definitions. Ann Intern Med 94:505, 1981
65. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Am J Med 96:200, 1994
66. Calvert CA. Valvular bacterial endocarditis in the dog. J Am Vet Med Assoc 180:1080, 1982
67. Feely J, Wilkinson GR, McAllister CB, et al. Increased toxicity and reduced clearance of lidocaine by cimetidine. Ann Intern Med 96:592, 1982
68. Drazner FH. Bacterial endocarditis in the dog. Compend Contin Educ 1:918, 1979
69. Erbel R, Rohmann S, Drexler M, et al. Improved diagnostic value of echocardiography in patients with infective endocarditis by transesophageal approach. A prospective study. Eur Heart J 9:43, 1988
70. Steckelberg JM, Murphy JG, Ballard D, et al. Emboli in infective endocarditis: the prognostic value of echocardiography. Ann Intern Med 114:635, 1991
71. Kim JH, Wiseman A, Kisslo J, et al. Echocardiographic detection and clinical significance of left atrial vegetations in active infective endocarditis. Am J Cardiol 64:950, 1989
72. Shively BK, Gurule FT, Roldan CA, et al. Diagnostic value of transesophageal compared with transthoracic echocardiography in infective endocarditis. J Am Coll Cardiol 18:391, 1991
73. Steckelberg JM, Murphy JG, Ballard D. Value of echocardiography in infective endocarditis. ACP Journal Club, 1991, p 27
74. Aragam JR, Weyman AE. Echocardiographic findings in infective endocarditis. *In* Weyman AE (ed): Principles and Practice of Echocardiography. 2nd ed. Philadelphia, Lea & Febiger, 1994, p 1178
75. Weyman AE, Griffin BP. Left ventricular outflow tract: the aortic valve, aorta, and subvalvular outflow tract. *In* Weyman AE (ed): Principles and Practice of Echocardiography. 2nd ed. Philadelphia, Lea & Febiger, 1994, p 498
76. Mugge A, Daniel WG, Frank G, et al. Echocardiography in infective endocarditis: reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. J Am Coll Cardiol 14:631, 1989
77. Pietro DA. The role of echocardiography in infective endocarditis. Echocardiography 2:423, 1985
78. Fregin GF, Luginbuhl H, Guarda F. Myocardial infarction in a dog. J Am Vet Med Assoc 160:956, 1972
79. Nielsen SW, Nielsen LB. Coronary embolism in valvular bacterial endocarditis in two dogs. J Am Vet Med Assoc 125:376, 1954
80. Murphy JG, Foster-Smith K. Management of complications of infective endocarditis with emphasis on echocardiographic findings. *In* Wilson WR, Steckelberg JM (eds): Infect Dis Clin North Am 1993, p 153
81. Washington JA. Blood cultures: principles and techniques. Mayo Clin Proc 50:91, 1975
82. Wilson WR, Van Scoy RE, Washington JA. Incidence of bacteremia in adults without infection. J Clin Microbiol 2:94, 1975
83. Weinstein MP, Murphy JR, Reller LB, et al. The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in

adults. II. Clinical observations, with special reference to factors influencing prognosis. Rev Infect Dis 5:54, 1983
84. Roberts FJ. The value of the second blood culture (correspondence). J Infect Dis 168:795, 1993
85. Ilstrup DM, Washington JA. The importance of volume of blood cultured in the detection of bacteremia and fungemia. Diagn Microbiol Infect Dis 1:107, 1983
86. Washington JA, Ilstrup DM. Blood cultures: issues and controversies. Rev Infect Dis 8:792, 1986
87. Chandrasekar PH, Brown WJ. Clinical issues of blood cultures. Arch Intern Med 154:841, 1994
88. Tonnesen A, Peuler M, Lockwood WR. Cultures of blood drawn by catheters vs venipuncture. J Am Med Assoc 235:1877, 1976
89. Bennett IL, Beeson RB. Bacteremia: a consideration of some experimental and clinical aspects. Yale J Biol Med 262:1, 1954
90. Anderson ET, Young LS, Hewitt WL. Simultaneous antibiotic levels in "breakthrough" gram-negative rod bacteremia. Am J Med 61:493, 1976
91. Crepin O, Roussell-Delvallez M, Martin GR, et al. Effectiveness of resins in removing antibiotics from blood cultures. J Clin Microbiol 31:734, 1993
92. Haskins SC. Management of septic shock. J Am Vet Med Assoc 200:1915, 1992
93. Dow SW, Curtis CR, Jones RL, et al. Bacterial culture of blood from critically ill dogs and cats: 100 cases (1985–1987). J Am Vet Med Assoc 195:11, 1989
94. Hirsh DC, Jang SS, Biberstein EL. Blood culture of the canine patient. J Am Vet Med Assoc 184:175, 1984
95. Calvert CA, Greene CE. Bacteremia in dogs: diagnosis, treatment, and prognosis. Compend Contin Ed 8:179, 1986
96. Hendershot EF. Fluoroquinolones. Infect Dis North Am 9:715, 1995
97. Balfour JA, Bryson HM, Brogden RN. Imipenem/cilastatin: an update of its antibacterial pharmacokinetics and therapeutic efficacy in the treatment of serious infections. Drugs 51:99, 1996
98. Bonow RO. Management of chronic aortic regurgitation. N Engl J Med 331:736, 1994
99. Scognamiglio R, Rahimtoola SH, Fasoli G, et al. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. N Engl J Med 331:689, 1994
100. Wideman FE, Blackstone EH, Kirklin JW, et al. Hospital mortality of re-replacement of the aortic valve. J Thorac Cardiovasc Surg 82:692, 1981
101. Bortolotti U, Milano A, Mazzucco A, et al. Results of reoperation for primary tissue failure of porcine bioprostheses. J Thorac Cardiovasc Surg 90:564, 1985
102. Cale AR, Sang CT, Campanella C, et al. Hufnagel revisited: a descending thoracic aortic valve to treat prosthetic valve insufficiency. Ann Thorac Surg 55:1218, 1993
103. Niederhauser U, von Segesser LK, Carrel TP, et al. Infected endocardial pacemaker electrodes: successful open intracardiac removal. PACE 16:303, 1993
104. White GL, White GS, Kosanke SD, et al. Therapeutic effects of prednisolone sodium succinate vs dexamethasone in dogs subjected to *E. coli* septic shock. J Am Anim Hosp Assoc 18:1, 1982
105. Hinshaw L, Peduzzi P, Young E, et al. Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. N Engl J Med 317:659, 1987
106. Bone RC, Fisher CJ, Clemmer TP, et al. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 317:653, 1987
107. Greenman RL, Schein RMH, Martin MA, et al. A controlled clinical trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of gram-negative sepsis. J Am Med Assoc 266:1097, 1991
108. Pennington JE. Therapy with antibody to tumor necrosis factor in sepsis. Clin Infect Dis 17(Suppl 2):S515, 1993
109. Durack DT. Current issues in prevention of infective endocarditis. Am J Med 78:149, 1985
110. Dajani AS, Bisno AL, Chung KJ, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. J Am Med Assoc 264:2919, 1990
111. Hupp JR. Changing methods of preventing infective endocarditis following dental procedures: 1943–1993. J Oral Maxillofac Surg 5:616, 1993
112. Wehrmacher EH. Myth: endocarditis. Arch Intern Med 154:129, 1994
113. van der Meer JTM, van Wijk W, Thompson J, et al: Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. Lancet 339:135, 1992

27 Myocardial Diseases of Dogs

DAVID SISSON
MICHAEL R. O'GRADY
CLAY A. CALVERT

CLINICAL IMPORTANCE

The cardiomyopathies are a group of diseases that primarily and predominantly affect the heart muscle. The primary cardiomyopathies, by definition, are idiopathic diseases that are not the result of an identifiable systemic disorder or any other type of congenital or acquired heart disease.[1] Patients with idiopathic myocardial disease are additionally classified into dilated, hypertrophic, and restrictive groupings based on the predominating functional and pathologic abnormalities detected clinically or at necropsy (Table 27–1).[1–6] Dilated cardiomyopathy is far and away the most prevalent form of cardiomyopathy in dogs.[2, 4, 7] Hypertrophic cardiomyopathy is, by comparison, an uncommon disorder, and restrictive cardiomyopathy is so rare that it is not recognized as a distinct clinical syndrome in dogs.[7] It has become fashionable in recent years to refer to the canine cardiomyopathies as breed-specific syndromes, e.g., Doberman, boxer dog, and cocker spaniel cardiomyopathy. This practice was prompted by breed-associated differences in presenting clinical signs, clinical course, and eventual outcome, and by the suspicion that the underlying cause of cardiomyopathy varies in different breeds.

Myocardial diseases resulting from well-defined disease processes are appropriately referred to as secondary myocardial diseases or as specific heart muscle diseases. The World Health Organization (WHO) classification scheme specifies that the term "cardiomyopathy" be used exclusively to designate only those myocardial diseases of unknown or uncertain etiology.[8] If the term is to be applied to a disorder with a defined etiology, it should at least be described by an appropriate modifier, such as hyperthyroid cardiomyopathy, ischemic cardiomyopathy, hypertensive cardiomyopathy, or taurine deficiency cardiomyopathy.[6] Those secondary myocardial diseases that have been reported in dogs and cats are listed in Table 27–1. Although the terminology and classification schemes described herein suffer from certain ambiguities and deficiencies, they provide an adequate framework for communicating the essential features of this constantly evolving group of diseases.

TABLE 27–1
Classification of Canine Myocardial Diseases

Primary Myocardial Diseases (Cardiomyopathies)
- Dilated cardiomyopathy
  - Breed-specific subcategories
    - Doberman pinschers
    - Boxer dogs
    - Cocker spaniels
    - Portuguese water spaniels
- Hypertrophic cardiomyopathy
  - Obstructive form
  - Nonobstructive form
- Restrictive cardiomyopathy (endomyocardial fibrosis)
- Unclassified (indeterminate) cardiomyopathy
  - Atrioventricular myopathy
  - Right ventricular cardiomyopathy

Secondary Myocardial Diseases
- Drugs and toxins
  - Anthracyclines—doxorubicin
  - Catecholamines
  - Ionophores
- Genetic
  - Canine X-linked muscular dystrophy (Duchenne's)
- Infiltrative
  - Glycogen storage diseases
  - Mucopolysaccharidosis
  - Neoplasia
- Ischemic
- Metabolic
  - Acromegaly
  - Diabetes mellitus
  - Hyperthyroidism
  - Systemic hypertension
    - Idiopathic
    - Renal disease
    - Hyperadrenocorticism
- Nutritional
  - Taurine deficiency
  - Vitamin E/selenium deficiency
  - L-Carnitine deficiency
- Inflammatory—myocarditis
  - Infectious—viral, protozoal, bacterial, fungal
    - Parvovirus, distemper virus
    - Chagas' disease, neosporosis, Lyme disease
  - Noninfectious

PRIMARY MYOCARDIAL DISEASES OF DOGS

CANINE DILATED CARDIOMYOPATHY

PREVALENCE AND DEMOGRAPHICS

Dilated cardiomyopathy (DCM) is one of the most common acquired cardiovascular diseases of dogs.[2, 4, 7, 9] Only degenerative valvular disease and, in some geographic regions, heartworm disease are more important causes of cardiac morbidity and mortality in dogs. The syndrome of canine dilated cardiomyopathy went unrecognized through the 1950s and much of the 1960s.[10] During the 1970s and early 1980s, the pathologic features of the most common types of myocardial disease in dogs and cats were described and categorized, and the clinical importance of these disorders was recognized. It was not until the introduction of echocardiography into clinical veterinary practice that a diagnosis of myocardial disease could be confirmed inexpensively and with a high degree of certainty on a routine basis. These studies established that large and giant breed dogs are particularly at risk for DCM, but that smaller breed dogs, such as cocker spaniels, may also be affected.

Surprisingly little information has been published documenting the prevalence of DCM. In 1988, an Italian study of 7148 dogs estimated the prevalence of DCM at 1.1 percent.[11] A more recent survey of 342,152 cases registered in the Veterinary Medical Data Base (VMDB) at Purdue from 1986 through 1991 indicated that the prevalence of canine DCM was 0.5 percent.[7] Depending on the precise criteria used, myocardial disease comprises 10 to 40 percent of the cardiology caseload in a teaching hospital environment (see chapter 23). The prevalence of canine dilated cardiomyopathy may be increasing owing to the rising popularity of certain predisposed breeds or, perhaps, because of the increased awareness of the practicing veterinarian.[9] It is interesting that the incidence of cardiomyopathy is also reported to be increasing in people.[12, 13]

In North America, canine DCM is diagnosed most often in the Doberman pinscher breed, and somewhat less often in other large and giant breed purebred dogs. This is reflected in the breed enrollment pattern of a recent therapeutic trial involving dogs with congestive heart failure due to DCM (Table 27–2).[14] However, in a recent Swedish study, Newfoundlands were diagnosed with DCM twice as often as any other breed (44/189 cases), followed by cocker spaniels (23/189 cases), Doberman pinschers (17/189), and Labrador retrievers (14/189).[15] Since the breed distribution of DCM cases varies by region in accordance with the popularity of the various predisposed breeds, it is use-

TABLE 27–2
Breed Distribution of Dogs with Dilated Cardiomyopathy Enrolled in the Enalapril Treatment Trial[14]

Breed	Frequency: No. of Dogs
Cocker spaniel	3 (4.1%)
Doberman pinscher	42 (56.8%)
German shepherd	4 (5.4%)
Great Dane	5 (6.8%)
Irish wolfhound	3 (4.1%)
Labrador retriever	4 (5.4%)
Old English sheepdog	3 (4.1%)
Terrier	1 (1.4%)
Other	9 (12.2%)
Total	74 (100%)

From Ettinger S, Lusk R, Brayley K, et al, for The Cooperative Veterinary Enalapril (COVE) Study Group. Evaluation of enalapril therapy in dogs with heart failure in a large multicenter study. Proceedings, 10th Annual Veterinarians Medical Forum, ACVIM 1992, p 584. Copyright 1992 Stephen J. Ettinger.

ful to know the prevalence of DCM within those breeds at greatest risk. In the 1986–1991 VMDB survey described earlier, the prevalence of DCM was 5.8 percent in Doberman pinschers, 5.6 percent in Irish wolfhounds, 3.9 percent in Great Danes, 3.4 percent in boxer dogs, 2.6 percent in Saint Bernards, 1.7 percent in Afghan hounds, 1.3 percent in Newfoundlands, and 0.9 percent in Old English sheepdogs (Fig. 27–1).[7] In a small population of Scottish deerhounds examined, the prevalence of DCM was 6.0 percent. By comparison, the prevalence of DCM was 0.69 percent in English cocker spaniels and 0.34 percent in American cocker spaniels. The prevalence rate of DCM in mixed breed dogs was approximately 0.16 percent compared with 0.65 percent in purebred dogs. Dilated cardiomyopathy was reported only rarely in dogs weighing less than 12 kg.

Dilated cardiomyopathy occurs in dogs of all ages, but the risk of DCM increases substantially with advancing age (VMDB, Fig. 27–2).[7] Owing to the smaller number of aged dogs examined, the majority of dogs presented for evaluation and treatment of heart failure due to DCM are between 4 and 10 years old. In contradiction to this general pattern, a new form of cardiomyopathy has recently been described that affects young (2- to 32-week-old) Portuguese water dogs.[16] Affected pups usually die within days following the onset of symptoms, and, as yet, there are no reported cases in adult dogs. Gender also appears to influence the risk of developing heart failure caused by DCM, at least in some breeds. This fact is evidenced by the 2:1 male/female ratio observed overall in the 1986–1991 VMDB survey, as well as in other studies.[7, 15, 17–23] In most published studies of Doberman pinschers with DCM, 70 percent to 80 percent of the dogs with signs of congestive heart failure were males.[19–23] In a recent report describing DCM in Dalmatians, all the affected dogs were males.[24] This pattern of male predominance is not observed in all affected breeds nor in asymptomatic dogs with occult disease.[24–27] In a study of 193 asymptomatic Doberman pinschers, O'Grady and Horne found no sex predilection either for subclinical myocardial dysfunction or for ventricular ectopia.[24] In a recent study of Newfoundlands with signs of heart failure due to DCM, 23 of 37 affected were females.[27] Nor is there an apparent sex predilection in the small numbers of cocker spaniels identified with DCM and a low plasma taurine concentration.[28] A recent study[29] of related boxer dogs suggests that cardiomyopathy in this breed is inherited as an autosomal dominant trait, reinforcing prior observations indicating no sex predilection.[25, 26]

PATHOLOGY

In most dogs dying of heart failure due to DCM, the heart is markedly enlarged and the myocardium appears pale, soft, and flabby. In Doberman pinschers and boxer dogs, dilation of the left atrium and left ventricle predominates (Fig. 27–3*A*), but in other breeds, such as Newfoundlands, Irish wolfhounds, and cocker spaniels, all chambers of the heart are grossly dilated.[3, 23, 25–27, 30–37] The ratio of left ventricular wall thickness to chamber diameter is decreased, and the circumferences of the annuluses of the mitral and tricuspid valves are increased in proportion to the magnitude of chamber dilation. The papillary muscles often appear flattened and atrophic. Depending on the age of the dog, the mitral and tricuspid valve leaflets may be midlly to moderately thickened and the chordae tendineae may be slightly thickened and elongated. These valvular changes are modest when compared with those observed in dogs dying from chronic valvular insufficiency caused by myxomatous degeneration (see chapter 25). The endocardium of the left atrium and ventricle is often mildly thickened. The presence and severity of myocardial hypertrophy is not always immediately evident due to the extremely

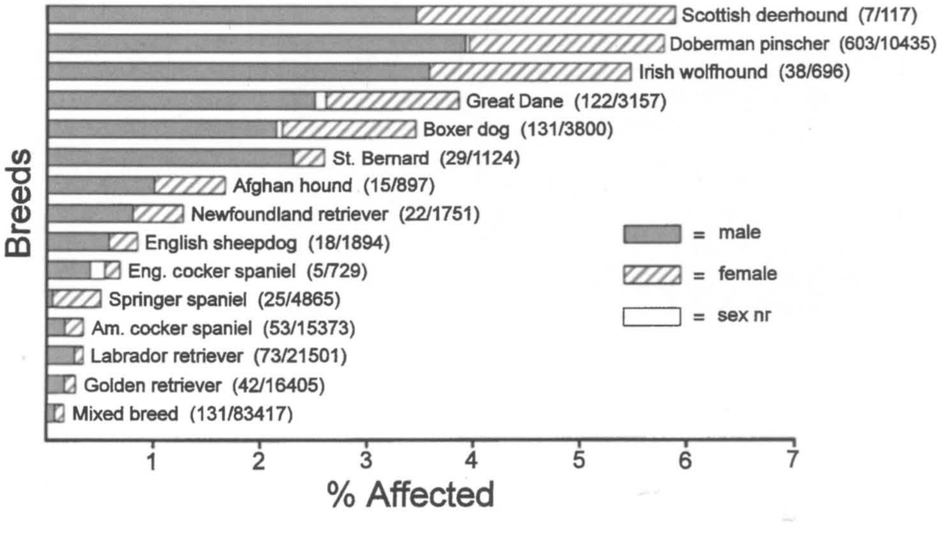


FIGURE 27–1

The prevalence of dilated cardiomyopathy (DCM), displayed as a percent of new hospital admissions, is highest in large and giant purebred dogs. Male predominance is observed in most but not all affected breeds. Source: Veterinary Medical Data Base (VMDB), Purdue University. (From Sisson DD, Thomas WP. Myocardial diseases. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 995.)

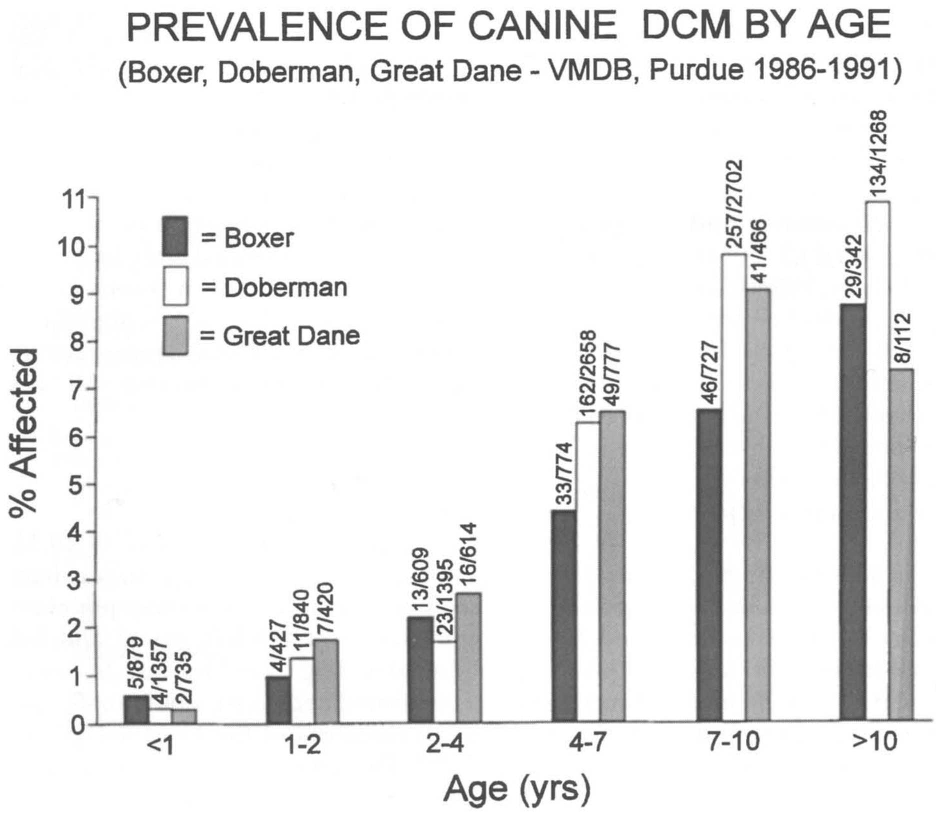


FIGURE 27–2

Prevalence of dilated cardiomyopathy by age group for the three most commonly affected breeds of dogs. Most breeds show increasing prevalence with advancing age. Source: Veterinary Medical Data Base (VMDB), Purdue University. (From Sisson DD, Thomas WP. Myocardial diseases. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 995.)

dilated chambers. Myocardial hypertrophy is best demonstrated and quantified by measurement of total heart weight and calculation of heart weight/body weight or heart weight/body surface area ratios. For example, in Newfoundlands dying of DCM, heart weight/body weight ratios varied from 193 to 292 gm/m^2, with a mean of 257 gm/m^2 (normal value = 120 gm/m^2).[27] Small, scattered areas of myocardial necrosis, hemorrhage, or fibrosis may be observed, but such lesions are usually not extensive.

Histologic changes observed in the myocardium of dogs dying from DCM are modest in relation to the severe degree of functional impairment observed clinically. Scattered foci of myocardial degeneration, with myocytolysis and vacuolization of myocytes, overt myocardial necrosis, and myocyte atrophy, are identified in

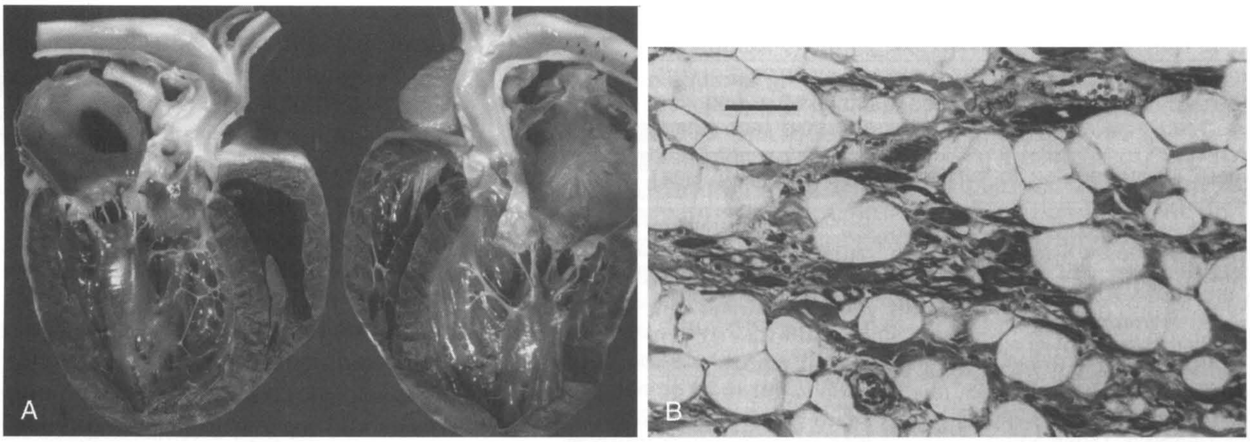


FIGURE 27–3

(A) Dilated cardiomyopathy heart from a Doberman pinscher. The left ventricle is markedly dilated, but the myocardium grossly appears normal. (B) This photomicrograph of the interventricular septum of a Doberman pinscher that died suddenly shows atrophied muscle fibers replaced by fibrous connective tissue. Trichrome stain; bar = 52 μm. (From Calvert CA, Hall G, Jacobs G, et al. Clinical and pathologic findings in Doberman pinschers with occult cardiomyopathy that died or developed congestive heart failure: 54 cases (1984–1991). J Am Vet Med Assoc 210:505, 1997.)

most dogs dying of DCM.[23, 27, 30–37] Damaged myocytes are replaced by varying amounts of fibrous or fatty tissue. Attenuated, wavy myofibers are a consistent and relatively specific histologic finding.[37a] Myocardial lesions are most pronounced in the base of the papillary muscles, in the interventricular septum, and in the subendocardial regions of the left ventricular free wall (Fig. 27–3*B*). There are no substantial differences in the histologic changes observed in dogs dying suddenly and those dying of congestive heart failure.[23] In boxer dogs, the right ventricular wall is the earliest and most severely affected region of the heart.[25] In advanced cases, widespread areas of myocardial fibrosis and fatty infiltration are observed. Remodeling of the intramural coronary arterioles is evidenced by intimal hyperplasia and extensive hypertrophy of smooth muscle cells in the media. Of particular note, inflammatory lesions are minimal or absent in most affected dogs dying of DCM. Small collections of cellular infiltrates, usually lymphocytes, plasma cells, and macrophages, are generally confined to focal areas of active myofiber necrosis.

Ultrastructural abnormalities described in dogs with DCM include scattered foci of degenerated myocardial cells exhibiting varying degrees of myocytolysis, mild to marked sarcoplasmic vacuolization, and increased intracytoplasmic collections of large, dense lipofuscin granules.[30–32] In more severely affected myocardial cells, the myofibrils are disrupted, disoriented, and loosely arranged in the cytoplasm together with large, scattered deposits of glycogen. Mitochondria are often increased in number and may be large and irregularly shaped, with abnormal or disrupted internal cristae.[30] These ultrastructural changes are generally regarded as nonspecific markers of cell damage. Pathologic studies to date have failed to identify the primary mechanism(s) responsible for reduced myocardial function in dogs with DCM.

ETIOLOGY/PATHOGENESIS OF DILATED CARDIOMYOPATHY

Proposed causes of canine DCM include viral infection, autoimmunity, myocardial toxins, microvascular hyperreactivity, nutritional deficiency, persistent or recurrent tachycardia, and a large number of genetic abnormalities.[1–7] It is likely that there are many different etiologies in dogs with DCM inasmuch as more than one primary disease process can induce the same functional and morphologic abnormalities.[37, 38]

Familial and Genetic Basis of DCM

The current consensus of opinion is that the majority of canine DCM cases have a familial or genetic basis, but the evidence for a genetic cause of DCM in dogs is by no means incontrovertible. The increased prevalence of myocardial disesase in Doberman pinschers, boxer dogs, Newfoundlands, cocker spaniels, Irish wolfhounds, and Great Danes certainly suggests a genetic basis for DCM in these breeds. Recent studies of boxer dogs with ventricular arrhythmia indicate that cardiomyopathy in this breed is inherited as an autosomal dominant trait.[29] Involvement of more than 50 percent of family members in some groups of Doberman pinschers (O'Grady, personal observation) argues strongly for a heritable predisposition or genetic abnormality in this breed as well. Most of the Doberman pinschers in the United States can be traced to one of seven closely related dogs, three of which died suddenly.[13, 39] Dilated cardiomyopathy in Portuguese water dogs appears to be inherited as an autosomal recessive trait.[16] The occurrence of idiopathic cardiomyopathy has also been tracked through three generations of English cocker spaniels and shown to be associated with a particular C4 phenotype.[40]

Twenty to thirty percent of human DCM cases are thought to be familial, and most demonstrate an autosomal dominant pattern of inheritance.[41, 42] Familial dilated cardiomyopathy in people appears to be a genetically heterogeneous disorder. Five different loci that cosegregate with the DCM have been mapped so far.[42] Currently, there is particular interest in genetic defects in the cytoskeletal proteins, including dystrophin and the dystrophin-related proteins.[43–45] Defects in the dystrophin gene are responsible for X-linked dilated cardiomyopathy in humans, and they are also responsible for Duchenne's and Becker's muscular dystrophies. Mutations in other cytoskeletal proteins, such as metavinculin, alpha-dystroglycan, alpha- and gamma-sarcoglycan, and muscle LIM protein, also result in dilated cardiomyopathy, suggesting that cytoskeletal proteins play an important role in cardiac function.[46]

Nutritional Abnormalities

TAURINE. It appears certain that taurine deficiency causes or contributes to the development of myocardial failure in a small proportion of the dogs with DCM, although this relationship is not as well established as in cats (see chapter 32).[28, 47, 48] The mechanism by which taurine deficiency induces myocardial failure is unknown. Taurine is the most abundant free amino acid in the heart and is thought to regulate intracellular calcium kinetics in some yet to be defined fashion. Taurine may also help eliminate oxygen free radicals in myocardial cells, thereby protecting the integrity of vital organelles and cell membranes. Kramer and associates found low plasma taurine concentrations (less than 25 nmol/ml) in 13/76 dogs with DCM, including 3/3 cocker spaniels and 4/6 golden

retrievers.[47] It is important to note that most dogs with DCM in this study, including 32/33 Doberman pinschers, had no evidence of taurine deficiency. A subsequent study showed that myocardial function improves in most cocker spaniels with DCM following supplementation with taurine and L-carnitine to the extent that traditional medical therapy for heart failure could be withdrawn without adverse effect.[28] Although the primacy of taurine deficiency in these cocker spaniels was confounded by the simultaneous supplementation of L-carnitine, we have achieved similar results using taurine alone. A recently published case study also indicates that L-carnitine is not needed to achieve a beneficial response.[49]

We have measured low plasma taurine concentrations in other breeds of dogs with DCM, including several mixed-breed dogs fed a vegetarian (lentil-based) diet. Myocardial function improved slowly but markedly over a 6-month period following taurine supplementation and a change to a more traditional diet. It is interesting that some dogs with DCM and a low plasma taurine concentration do not improve following taurine supplementation. The relationship between taurine-associated DCM in American cocker spaniels and DCM in English cocker spaniels is unknown. Myocardial function improves substantially in some American and English cocker spaniels with low plasma taurine concentrations after treatment using only conventional medications (digoxin, diuretics, and ACE inhibitors without supplemental taurine). In some of these patients, plasma taurine concentrations rise into the normal range without the benefit of taurine supplementation (personal communication, Dr. Matt Miller, Texas A&M). Nonetheless, it seems prudent to administer taurine to those dogs with DCM and a confirmed low plasma or blood taurine concentration.

L-CARNITINE. The notion that carnitine deficiency might cause DCM in dogs was first advanced by Keene.[50] He subsequently demonstrated reduced myocardial concentrations of free carnitine in 50 percent to 90 percent of dogs with DCM, including some boxer dogs, Doberman pinschers, Samoyeds, and American cocker spaniels.[51–55] Since plasma carnitine levels do not accurately reflect myocardial carnitine content, endomyocardial biopsies were required to demonstrate this deficiency. The hypothesis that carnitine deficiency might be a cause of canine DCM was attractive for several reasons. First, a heritable form of DCM in humans had already been shown to result from an inborn error of carnitine metabolism, and second, carnitine is known to play an essential role in cardiac metabolism, acting to shuttle long chain free fatty acids into the mitochondria in the form of esters of acylcarnitine.[55] Long chain free fatty acids represent the most important substrate for myocardial energy needs. In addition, carnitine functions as a detoxifying agent within the mitochondria, where it binds acyl groups and other toxic metabolites accumulating as a result of normal mitochondrial activity and transports them out of the mitochondria as esters of carnitine.

Myocardial carnitine levels are reduced in the majority of cardiac disorders of people, suggesting that myocardial carnitine concentrations often decline simply as a consequence of heart failure.[56] The same is probably true in dogs, and there is little accumulated evidence to suggest that a deficiency of carnitine causes DCM. There is evidence that carnitine supplementation can exert a modest beneficial effect in heart failure, presumably by replenishing depleted myocardial stores.[57] There is little evidence to suggest that carnitine supplementation reverses the primary myocardial dysfunction responsible for heart failure in the great majority of dogs with DCM. Pre-existing cardiac arrhythmias are not abolished and sudden death is not prevented by L-carnitine supplementation. In one report, carnitine supplementation in two boxer dogs did not produce any measurable clinical benefit.[58]

OTHER NUTRITIONAL DISORDERS. There have been no published studies assessing the potential role of other micronutrients in the etiology of cardiomyopathy. Thus, the role of thiamine, selenium, cobalt, phosphorus, calcium, and iron remains unknown. It has been suggested that a deficiency of coenzyme Q10 (CoQ10, or ubiquinone) might be responsible for DCM in people (and/or dogs) and that it might be effective in palliating these patients.[59] Although there is no definitive evidence for an etiologic role for coenzyme Q10, some experimental evidence indicates that it exerts a modest beneficial effect in heart failure, perhaps as a result of its antioxidant properties.[60]

Viral Causation

With the exception of parvovirus, serious investigation into the potential role of viruses in canine DCM has not taken place. In humans, viral infection is suspected as one of the most common causes of DCM.[1, 61–64] The enteroviruses, particularly the coxsackieviruses, are most frequently identified in people in this setting.[64] The role of viral infections in DCM has been difficult to establish in human patients because evidence of the putative viral infection is usually absent by the time frank congestive heart failure manifests. With the advent of improved virus identification methodologies, evidence of viral nucleic acid in patients with DCM has provided stronger evidence for a prior viral infection.[65] The absence of widespread inflammation or extensive myocardial damage in most dogs and humans dying from DCM certainly argues against a viral etiology and supports the hypothesis that one or

more subcellular metabolic abnormalities is responsible for the development of myocardial failure.[66, 67]

Immune-Mediated Disorders

An emerging body of evidence suggests that DCM might be the consequence of immunologic processes. Circulating heart-specific autoantibody,[68] antibody directed against the beta-adrenergic receptor,[69, 70] antibody directed against the ADP-ATP mitochondrial translocator protein,[71] and antibody against alpha- and beta-cardiac myosin heavy chain protein[72] have been implicated in the pathogenesis of DCM either in humans or in experimental animals. Immune-mediated phenomena seem to play a particularly important role in dogs with chronic myocarditis, e.g., Chagas' disease.[70] Cardiomyopathy in English cocker spaniels is associated with circulating antimitochondrial antibody and other immunologic abnormalities.[40] Antibodies against the alpha-helical structures of bacterial and viral antigens can also cause immune-mediated heart disease.[73] Thus, molecular mimicry may be an important mode of immunologic cardiac attack. Drug-induced cardiotoxicity may also alter the antigenicity of myocytes sufficiently to induce immune reactivity to new antigenic epitopes.[74] It is not clear whether autoantibodies directed against cardiac antigens are important in the genesis of myocardial failure or whether they are simply produced as a consequence of cellular damage. Specific HLA antigens are associated with DCM in people.[75] Other immunologic abnormalities identified in people with DCM include reduced suppressor T-cell function and excess T-helper cell activity.[76, 77]

Tachycardia-Induced Myocardial Failure

Sustained tachycardia, induced by rapid artificial pacing, is a commonly used method for creating experimental heart failure in dogs.[78, 79] Dogs develop congestive heart failure when their hearts are artificially and continuously paced at 240 beats per minute for 3 to 4 weeks.[80] Death from myocardial failure typically occurs at 4 to 6 weeks. Tachycardia increases myocardial oxygen demand yet reduces the time available for ventricular filling and coronary perfusion. Neurohumoral responses, similar to those observed in spontaneously occurring heart failure, are evoked, resulting in remodeling of the coronary vasculature, a reduced volume fraction of capillaries, and severely impaired myocardial function.[81, 82] Rapid cardiac pacing eventually causes a substantial percentage of myocardial cells to die while inducing a deficit in contractility in the remaining cells.[83, 84] Long-standing atrial fibrillation, ventricular tachycardia (VT), or supraventricular tachycardia (SVT) can also produce reversible myocardial dysfunction, with the severity of myocardial dysfunction depending on the type of tachycardia, the heart rate, and the duration of the tachycardia.[85, 86] Labrador retrievers are predisposed to persistent or recurrent supraventricular tachycardia, and some affected dogs develop profound myocardial failure in association with the arrhythmia.[87] In some but not all cases, myocardial failure resolves with abolition of the tachycardia. Some giant breed dogs, including Irish wolfhounds and Great Danes, often present with atrial fibrillation and no or only modest ventricular dysfunction. Myocardial failure eventually develops in these patients, and it is unclear whether this outcome is a consequence of chronic atrial fibrillation or simply represents progression of an underlying myopathic process.

PATHOPHYSIOLOGY

The predominant physiologic abnormality in DCM patients is impaired systolic ventricular function caused by declining myocardial contractility. Impaired systolic function is reflected by the decreased rate of ventricular pressure development (dp/dt), reduced ejection-phase indices (ejection fraction, fractional shortening, rate of ejection), and increased end-systolic volume. Diastolic ventricular function, as reflected in measures of left ventricular compliance, is also abnormal in dogs with DCM. Together, these functional disturbances result in elevated ventricular end-diastolic, atrial, and venous pressures, and ultimately in congestive heart failure. Marked reductions in ventricular stroke volume result in systemic arterial hypotension and signs of low output failure, manifested as weakness, exercise intolerance, syncope, or cardiogenic shock. Valvular insufficiency, cardiac arrhythmia, and neurohormonal compensatory responses contribute to ventricular dysfunction and signs of cardiac failure in dogs with DCM (see chapters 11, 12). Mitral and tricuspid insufficiency develop in most dogs with DCM, as demonstrated by Doppler echocardiography. In most cases, the magnitude of regurgitation is usually mild, but moderate to severe mitral regurgitation can occur, particularly in those dogs with concurrent valvular degeneration.

BIOCHEMICAL ALTERATIONS. The precise mechanisms of cardiac dysfunction at the cellular level remain unidentified in dogs with DCM. It is particularly difficult to establish whether an observed biochemical abnormality is the principal cause of myocardial dysfunction or a more general consequence of cellular damage or adaptive change to the heart failure state. Alterations in myocyte energetics are believed by many investigators to be responsible for reduced contractility in patients with DCM. Reduced energy reserves, as indicated by a reduced creatine phosphate-to-ATP ratio, have been demonstrated in people with DCM.[88] Disorders of energy supply and reduced availability of ATP

would have a profound effect on systolic and diastolic function. Morphologic changes in myocardial mitochondria have been observed in dogs with DCM and in patients with heart failure from many causes.[30, 31, 89] Although most of these changes are regarded as secondary alterations, primary mitochondrial defects are suspected as the cause of heart failure in at least one familial form of DCM in humans.[90–92]

O'Brien and colleagues have suggested that the primary metabolic defect in Doberman pinscher DCM is aerobic energy production.[93, 94] These investigators documented impaired oxidative production of ATP in Doberman pinschers with DCM and showed that myocardium from Dobermans with DCM has a 50 percent reduction in mitochondrial electron transport activity and a 90 percent reduction in myocardial myoglobin concentration.[94, 95] They further showed that these changes were associated with decreased myocardial ATP concentration and intracellular acidosis.[95] The same investigators have demonstrated modest reductions in myofibrillar and mitochondrial creatine kinase activity in the myocardium of Doberman pinschers with DCM, and even more profound reductions in cytosolic creatine kinase activity.[93]

Since relaxation is an energy-dependent process, reduced myocyte energy stores might also be responsible for the diastolic functional abnormalities observed in DCM patients. Myocardial relaxation occurs when the activator calcium pool is removed from the cytosol. Calcium transport from the cytosol to the sarcoplasmic reticulum is an energy-dependent process. The rapid reduction in cytosolic calcium causes dissociation of calcium from troponin, causing tropomyosin to revert back to its resting inhibitory conformation. ATP then binds myosin, causing dissociation of the actin-myosin cross-bridges and relaxation. Removal of calcium from the cytosol is initially accomplished by the sarcoplasmic reticulum Ca^{2+}-ATPase pump.[96] The activity of this enzyme is controlled by the regulatory protein phospholamban. Calcium uptake by the sarcoplasmic reticulum is increased by phosphorylation of phospholamban. The sarcoplasmic reticulum Ca^{2+}-ATPase pump is further modulated by an allosteric effect of ATP.[96, 97] High concentrations of ATP induce the uptake of calcium by the sarcoplasmic reticulum, while low ATP concentrations retard calcium removal from the cytosol. Cytosolic calcium levels are also regulated by the sarcolemmal sodium-calcium exchanger.[96] This mechanism is dependent on the ATP-dependent sodium-potassium pump. Thus, ATP is important to the function of both the sarcoplasmic reticulum Ca^{2+}-ATPase pump and the sarcolemmal sodium-calcium exchanger via the sodium-potassium pump.

Some investigators believe that alterations in peak activator calcium levels mediate myocardial systolic dysfunction in DCM patients.[98, 99] Abnormalities of cyclic AMP (cAMP) production,[100] the sarcolemmal L-type channels,[101, 102] or the sarcoplasmic reticulum calcium release channel[103] could cause a reduction of cytosolic activator calcium. Calcium release channel (CRC) activity is reduced in dogs with DCM owing to decreased activity of Ca^{2+}-ATPase, decreased CRC content, and inhibition.[104] Decreased production of cAMP in the setting of DCM could occur from inhibition of the stimulatory G protein[105] or an increase in the inhibitory G protein.[106, 107] Other investigators maintain that the level of activator calcium is normal in failing hearts.[100] Other studies suggest that the loss of contractility in DCM patients results from a decrease in the sensitivity of the myofilaments to activator calcium, and that this effect is due to increased cytosolic concentrations of inorganic phosphorus and hydrogen ions.[108, 109]

Other biochemical abnormalities found in the myocardium of dogs with DCM include reduced myocardial carnitine concentrations,[53, 55] decreased beta-receptor–mediated adenylate cyclase activity,[110] and elevated myocardial concentrations of promatrix metalloproteinase-9 and neutrophil elastase.[111] This change could play a fundamental role in the development of DCM, inasmuch as myocardial function is profoundly influenced by the structural integrity of the extracellular matrix.

INFLUENCE OF ARRHYTHMIA. Cardiac arrhythmia, such as atrial fibrillation and ventricular tachycardia, is frequently detected in dogs with DCM. The development of atrial fibrillation has important immediate and chronic consequences for dogs with underlying heart disease. Cardiac output declines by as much as 25 percent in healthy dogs with induced atrial fibrillation as a result of decreased and irregular diastolic filling times and the loss of atrial and ventricular synchronization.[112, 113] Darke[114] has shown that stroke volume is severely reduced in dogs with DCM and atrial fibrillation when the R-R interval is less than 0.30 second. With the development of atrial fibrillation, right and left atrial pressures increase, and, as a result, rapid decompensation may occur when dogs with DCM develop atrial fibrillation, particularly if the heart rate is greater than 200 beats per minute. Chronic atrial fibrillation may also be an important contributing cause of progressively deteriorating myocardial contractility. Based on studies of humans with DCM, atrial fibrillation may also be an important contributing cause of sudden death.[115] Sustained ventricular arrhythmia can cause profound circulatory embarrassment, collapse, and sudden death. The frequency and severity of ventricular arrhythmia observed in boxer dogs and Doberman pinschers with DCM may also be indicative of the likelihood of sudden death.[19–26, 116]

CLINICAL PRESENTATION

The spectrum of clinical signs exhibited by dogs with DCM is similar in all breeds, but the observed

frequency of these signs is conspicuously different in many of the commonly affected breeds. Doberman pinschers and boxer dogs generally present for signs of acute left-sided heart failure, such as coughing and dyspnea; or for signs attributable to some life-threatening arrhythmia, such as syncope, episodic weakness, or collapse.[20, 25] Sudden death may be the first observed sign in dogs with DCM. Twenty percent to thirty percent of Doberman pinschers and boxer dogs with DCM die suddenly, often during the first or second episode of collapse. The remaining dogs either die or are euthanized because of heart failure or some other intercurrent event. Of those Doberman pinschers developing end-stage heart failure, three-fourths present with isolated left heart failure whereas one-fourth manifest signs of biventricular failure (pulmonary edema, ascites, ± pleural effusion or peripheral edema).[22] Other large and giant breed dogs are much less likely to experience syncope or to die suddenly, and they are more likely to present with ascites and/or pleural effusion than Dobermans or boxers. In a recent study of Newfoundlands with DCM, ascites was observed in 35 percent of the dogs.[27] This finding is even more prevalent in other giant breed dogs. These dogs usually have marked left ventricular dysfunction as well, but pulmonary congestion is usually less severe compared with that observed in Doberman pinschers. Some dogs with DCM are presented because of subtle evidence of exercise intolerance, and a small percentage of dogs with DCM are identified during a physical examination for some unrelated problem. In such cases DCM is often detected incidentally with the discovery of an arrhythmia, gallop rhythm, or systolic murmur.

PHYSICAL EXAMINATION

Most dogs with clinical signs due to DCM manifest conspicuous evidence of their underlying heart disease that is detectable by a carefully conducted physical examination. Low-pitched, protodiastolic (S_3) gallop sounds are a frequent and important clinical finding. This transient heart sound is most easily appreciated in dogs in sinus rhythm but can also be heard clearly, if intermittently, in most dogs with atrial fibrillation. An S_3 gallop sound is strong evidence of severe ventricular impairment.[117–119] In about one half of dogs with DCM, a soft regurgitant systolic murmur, typically grade 1 to 3/6, is audible over the mitral and/or tricuspid valve regions. Careful auscultation of the heart also often reveals an irregular rhythm because of the presence of isolated ventricular or supraventricular premature beats, paroxysmal ventricular or supraventricular tachycardia, or atrial fibrillation. Atrial fibrillation occurs most frequently in giant breed dogs, such as Irish wolfhounds, Newfoundlands, and Great Danes. By contrast, premature ventricular beats and ventricular tachycardia are more likely to be detected in Doberman pinschers and boxer dogs. Both breeds occasionally experience complete heart block.[25, 26, 120] A variety of other arrhythmia and conduction disturbances can develop in dogs with DCM, underscoring the importance of electrocardiographic (ECG) evaluation of all affected dogs.

Weak and rapid arterial pulses are detected in the majority of dogs with DCM. The markedly irregular pulse and accompanying pulse deficits are obvious in dogs with frequent premature beats or atrial fibrillation. Pulsus alternans, an alternating arterial pulse amplitude in the absence of cardiac arrhythmia, is a more subtle and less common finding that usually signifies profound myocardial failure. Rales, crackles, and increased bronchovesicular lung sounds are evident in many dogs with left-sided heart failure and pulmonary edema. In some dogs, crackles are heard only at end-inspiration over the hilar region. In more severely affected dogs, these sounds can be heard over all lung fields. Jugular venous distention, jugular pulses, hepatomegaly, and ascites are detectable in most dogs with right-sided or biventricular heart failure. In contrast to other species, peripheral edema occurs rarely in dogs and only with profound heart failure. The heart and lung sounds are sometimes muffled as a result of pleural effusion. Weight loss and muscle wasting are common in some dogs with DCM, but the majority of dogs have normal muscle mass and body fat when they first present. Weight loss and muscle atrophy are more dramatic in dogs that have been symptomatic for several months.

LABORATORY FINDINGS

A complete blood count (CBC), blood chemistry profile, and urinalysis are prudently performed in dogs with DCM in order to detect other concurrent diseases and to guide therapy. Serum biochemical alterations observed in Doberman pinschers with CHF and also seen in other breeds include a moderate increase in alkaline phosphatase, often with no increase in ALT (alanine transaminase) or AST (aspartate transaminase), a mild reduction in globulins with no or only a modest decline in serum albumin, a mild increase in creatinine and urea, a mild reduction in amylase, a moderate reduction in the anion gap, and a mild reduction in sodium.[121] An occasional dog with profound heart failure may exhibit hyperkalemia in association with hyponatremia, falsely suggesting Addison's disease. The CBC findings are not different from those of normal dogs except for a moderate lymphopenia and occasionally a modest neutrophilia. Blood gas analysis or pulse oximetry determinations are particularly useful for monitoring therapeutic responses in animals with severe heart failure. Other tests have more limited clinical utility. The taurine concentration in blood or plasma should be determined whenever

the patient is a cocker spaniel or golden retriever, the diet is unusual, or the breed is atypical. Inasmuch as thyroidal illness does not appear to be associated with DCM, little is to be gained by routinely evaluating thyroid function in dogs with DCM.[122]

ELECTROCARDIOGRAPHIC ABNORMALITIES

Resting ECGs recorded from dogs with DCM are usually abnormal. Widened or high-amplitude QRS complexes, indicating left ventricular enlargement, and widened P waves, indicating left atrial enlargement, are noted in one third to one half of dogs with DCM. It is important to note that these criteria are lacking in many affected dogs, and some dogs with CHF demonstrate low voltage (1.0 to 1.2 mv or less) R waves and slurring of the R-wave downstroke.[123] The mean electrical axis of the QRS in the frontal plane is usually normal. Cardiac rhythm disturbances are common in all breeds developing DCM, but the nature and prevalence of different arrhythmias vary in different breeds (Table 27–3). For this reason, cardiac arrhythmias are appropriately discussed in the context of breed. The sensitivity of ECG recordings for detecting arrhythmia also varies with the duration of the recording. Continuous ambulatory ECG recordings, often referred to as Holter recordings, are performed on patients during their regular activity. They offer an ideal, noninvasive means to quantify the frequency and complexity of any arrhythmia over an extended period of time, typically 24 hours, although a 6-hour recording may be ample in some circumstances.[124] Holter recordings are particularly useful in Doberman pinschers and boxer dogs, which tend to manifest frequent ventricular arrhythmias. They can be used to correlate the presence or absence of arrhythmia with the patient's symptoms, and to assess the efficacy of antiarrhythmic medication.[125]

TABLE 27–3
Prevalence of Cardiac Arrhythmias and Conduction Disorders in Boxer Dogs, Doberman Pinschers, and Newfoundlands with Dilated Cardiomyopathy

	Prevalence (% Affected)		
	Boxers (n=112)	*Dobermans (n=39)*	*Newfoundlands (n=31)*
Supraventricular Arrhythmias			
Premature depolarizations	18.8	7.7	NR
Atrial tachycardia	8.0	NR	NR
Atrial fibrillation	10.7	17.9	45.2
Ventricular Arrhythmias			
Premature depolarizations	45.5	92.3	16.0
Ventricular tachycardia	38.4	40.0	NR
Conduction Disturbances			
Left bundle branch block	2.7	NR	NR
Complete A-V block	2.7	NR	NR

NR = not reported.

From Harpster NK. Boxer cardiomyopathy—A review of the long-term benefits of antiarrhythmic therapy. Vet Clin North Am Sm Anim Prac 21:989, 1991; Calvert CA. Dilated congestive cardiomyopthy in Doberman pinschers. Compend Cont Educ 8:417, 1986; and Tidholm A. Dilated cardiomyopthy in the Newfoundland: A study of 37 cases (1983–1994). J Am Anim Hosp Assoc 32:465, 1996.

DOBERMAN PINSCHERS. Ventricular premature complexes (VPCs) and ventricular tachycardia are recorded in more than three-fourths of Doberman pinschers with CHF due to DCM.[20] In a recent study of Doberman pinschers that subsequently died suddenly or developed CHF, ventricular arrhythmias were documented in 100 percent of the dogs, using 24-hour Holter recordings.[23] Most other large and giant breed dogs with DCM do not exhibit VPCs as often, nor do they experience complex ventricular arrhythmia as frequently as Doberman pinschers. By comparison, atrial fibrillation is observed in only 15 percent to 30 percent of Doberman pinschers with CHF and DCM.[126] This is a lower occurrence rate than is observed in many other large and giant breed dogs. Ventricular premature complexes are also commonly recorded in asymptomatic Doberman pinschers. In two studies of 193 and 103 asymptomatic Doberman pinschers, the frequency of VPCs observed on a resting ECG or during a subsequent echocardiogram was 13.5 percent and 14 percent, respectively.[24, 126] Holter recordings of asymptomatic Doberman pinschers show an even higher occurrence rate.[127] A further discussion of the incidence of ventricular arrhythmia in Doberman pinschers can be found in the section describing occult DCM.

BOXER DOGS. Ventricular arrhythmias are also very prevalent in boxer dogs with cardiomyopathy. In contrast to Doberman pinschers, boxer dogs commonly manifest ventricular arrhythmia with no echocardiographic evidence of myocardial dysfunction when they initially present. Ventricular arrhythmias are observed in as many as 84 percent of boxers diagnosed with DCM, and most affected dogs have more than 20 VPCs/min.[25, 26] The morphology of VPCs in boxer dogs is quite characteristic in that the configuration of the complexes is almost always consistent with a right ventricular origin (a wide and predominately positive QRS deflection in leads I, II, III, V_3, and V_4, and a predominately negative QRS deflection in lead V_1). Monomorphic VPCs are 2.5 times more common than multiform VPCs in this breed. Paroxysmal ventricular tachycardia occurs in about one third of affected boxer dogs. The prevalence of atrial fibrillation is reported to be only 11 percent in boxers with cardiomyopathy, but the study population included many dogs without signs of CHF.[25, 26] Infrequent ECG abnormalities detected in this breed include paroxysms of supraventricular tachycardia (7 percent) and third-degree atrioventricular heart block (3 percent).

OTHER LARGE AND GIANT BREEDS. Overall, other large and giant breed dogs with DCM seem to experience much fewer and less serious ventricular arrhythmias than Doberman pinschers and boxer dogs, and they also seem to experience a much lower rate of sudden death. Atrial fibrillation, however, is a particularly common rhythm disturbance that is recorded in as many as 75 percent to 80 percent of giant breed dogs with DCM.[2–5, 7, 112] In one study, only 16 percent of the Newfoundlands evaluated had VPCs, and none had documented episodes of ventricular tachycardia, but 45 percent of these dogs had atrial fibrillation (see Table 27–3).[27]

RADIOGRAPHIC CHANGES

Thoracic radiographs are obtained in dogs with DCM to evaluate heart size and to determine the presence and severity of pulmonary edema or pleural effusion. Generalized cardiomegaly is the usual finding in most large and giant breed dogs with DCM and in cocker spaniels (Fig. 27–4). Evidence of biventricular heart failure, including pulmonary edema, an enlarged caudal vena cava, hepatomegaly, and ascites, is typical in these breeds. In some cases there is a substantial volume of pleural effusion. Cardiomegaly is less impressive in most Doberman pinschers and boxer dogs with DCM than in many other breeds. Heart size should not be used as a measure of the severity of myocardial failure, as there is little correlation between radiographic heart size and clinical outcome.

Left atrial enlargement and pulmonary edema are the most prominent radiographic changes in Dobermans and boxer dogs with DCM (Fig. 27–5). Good-quality radiographs are required to determine accurately the presence and severity of pulmonary edema. Early (mild) pulmonary congestion is sometimes confused with other disorders such as chronic bronchitis, particularly when prominent peribronchiolar cuffing is visible on the thoracic radiographs. This radiographic finding often reflects the accumulation of edema fluid in the walls of the bronchi and bronchioles. Close inspection of the radiographs typically reveals distended pulmonary veins and loss of definition of the margins of the pulmonary vessels. These vessels lose their crisp definition as fluid accumulates in the perivascular lymphatics and the interstitium. The identification of more severe pulmonary edema is less problematic as the perihilar distribution of fluid becomes more apparent and air bronchograms become visible.

ECHOCARDIOGRAPHY

Echocardiography is essential to establish the diagnosis of DCM and to define the extent of systolic and diastolic dysfunction. It is the best available way definitively to exclude other causes of heart disease, such as acquired valvular or pericardial disease. Chamber dilation and reduced myocardial contractility are the hallmarks of DCM, and these abnormalities can be quickly quantified by M-mode or two-dimensional echocardiography (Fig. 27–6).[4, 21–24, 114, 116, 126, 128] Short-axis end-systolic and end-diastolic dimensions of the left ventricle, indexed for body weight, are increased in dogs with DCM. Diastolic ventricular wall thickness measures are usually in the normal range, although

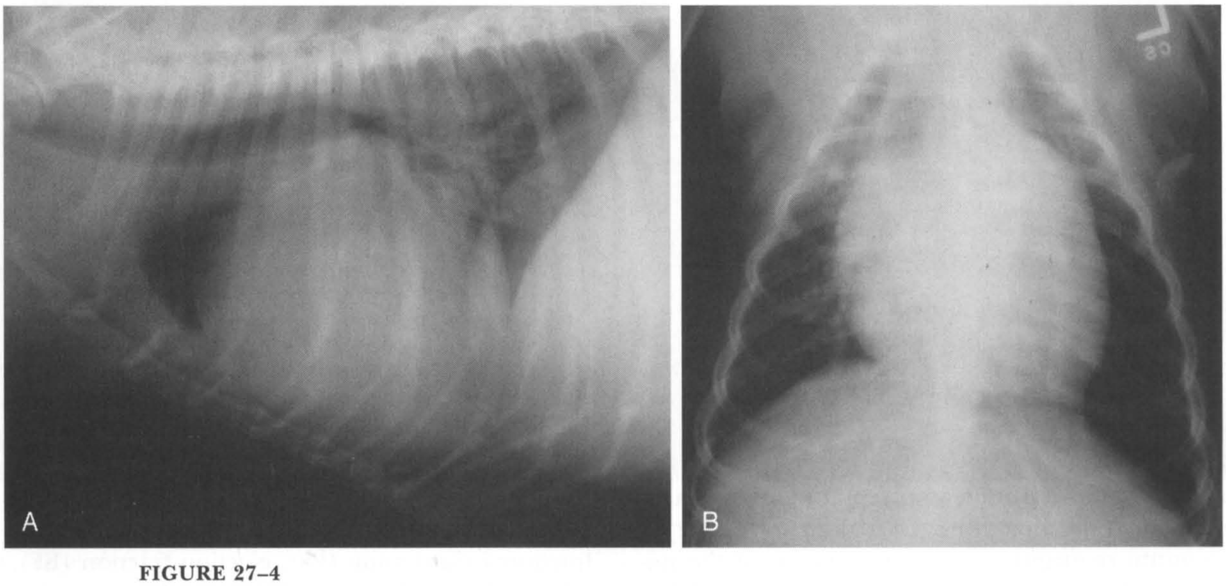


FIGURE 27–4

Lateral (A) and dorsoventral (B) radiographs from an American cocker spaniel with DCM show biventricular and biatrial enlargement. (From Sisson DD, Thomas WP. Myocardial diseases. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 995.)

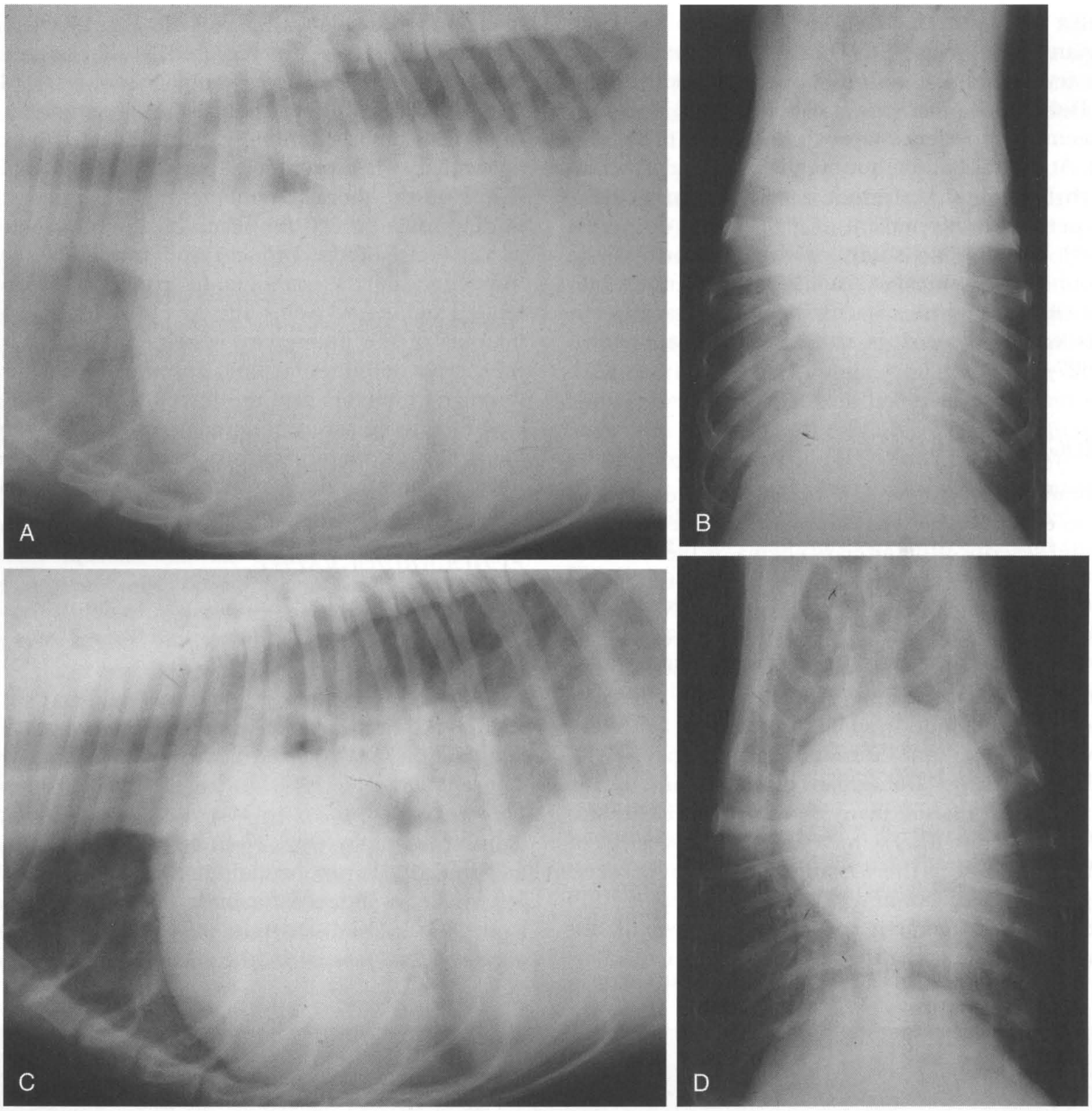


FIGURE 27–5

This series of lateral (A,C,E) and dorsoventral (B,D,F) radiographs is from a Doberman pinscher with dilated cardiomyopathy. Cardiac enlargement is predominantly left sided, and severe perihilar pulmonary edema is evident prior to treatment (A,B). Twenty-four hours after treatment with IV furosemide and continuous infusions of nitroprusside and dobutamine, the pulmonary edema has lessened (C,D).

dilation of the chambers makes the walls of the heart appear thin. Failure of the walls of the LV to thicken normally contributes to this effect. Global and symmetric left ventricular hypokinesis is observed in most dogs with DCM. Asymmetric contraction of the left ventricular walls, with increased septal wall motion, is observed in some dogs with DCM and moderate to severe mitral regurgitation. The excursions of the mitral valve leaflets are often diminished because of low cardiac output and decreased venous return. Mitral valve closure may be delayed owing to markedly elevated ventricular filling pressures. The left atrium is usually dilated, and this finding can be quickly normalized by calculation of the left atrial/aortic ratio. Right atrial and ventricular dimensions are increased in those dogs experiencing biventricular failure, but such findings are often absent in boxer dogs and Doberman pinschers.

The systolic ejection phase indices, including LV fractional shortening (FS), ejection fraction (EF), and velocity of circumferential fiber (VCF) shortening, are decreased in proportion to the severity of systolic dysfunction. In most affected dogs, these contractile indices are profoundly depressed at the time of initial

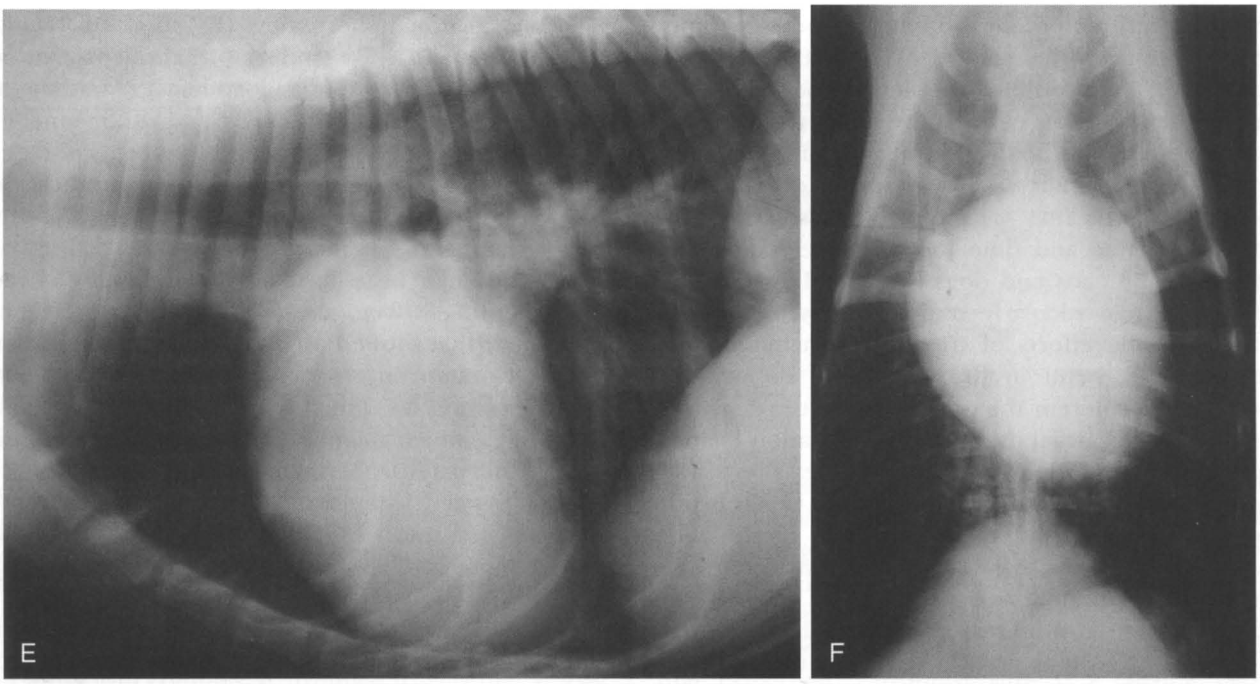


FIGURE 27–5 *Continued*

Forty-eight hours after treatment was initiated, the pulmonary edema has resolved and the enlarged heart is more clearly seen (E,F).

presentation. Fractional shortening is often in the range of 12 percent to 15 percent and changes very little once overt congestive heart failure has developed. The distance between the mitral valve at its maximal opening (E) point in early diastole and the interventricular septum (EPSS, E-point septal separation) is increased as a reflection of a low ejection fraction. Systolic time intervals (STIs), including left ventricular ejection time (LVET) and pre-ejection period (PEP), can also be determined to quantify the degree of left ventricular dysfunction and to evaluate medical interventions.[129, 130] In dogs with DCM, potent positive inotropic drugs can increase the duration of a reduced LVET and will shorten a prolonged PEP.

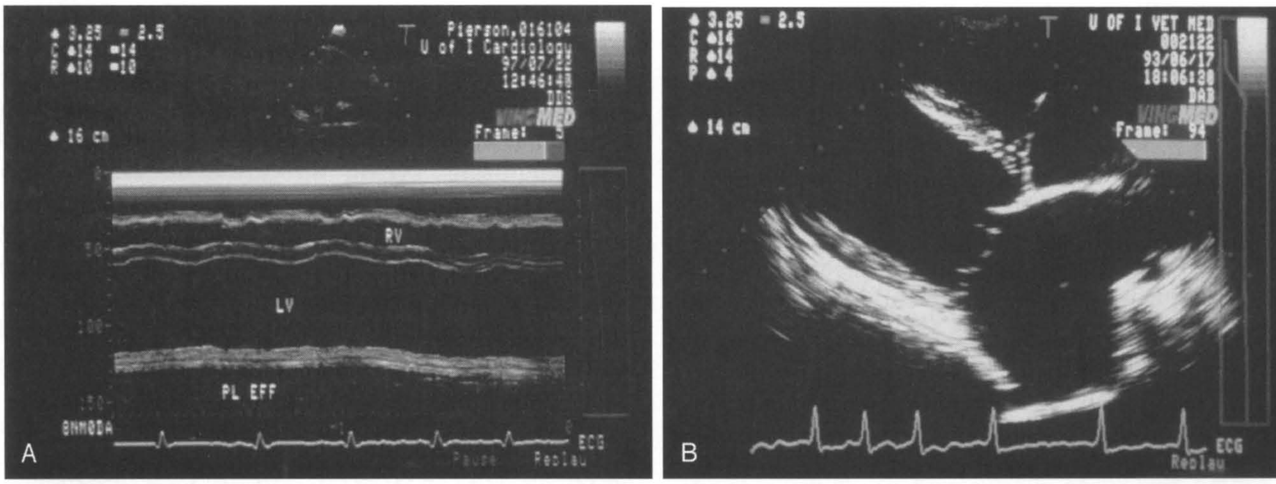


FIGURE 27–6

M-mode (A) and two-dimensional (B) echocardiograms from two Doberman pinschers with dilated cardiomyopathy. (A) The M-mode recording was obtained from a Doberman pinscher with biventricular heart failure and shows a dilated right ventricle and left ventricle at a level just below the mitral valve leaflets. Fractional shortening is markedly decreased, and the amplitudes of the LV free wall and interventricular septum are diminished. Pleural fluid surrounds the heart echoes. (B) The two-dimensional echocardiogram from another Doberman pinscher was obtained at end-systole and demonstrates dilated atria and increased end-systolic dimensions of the left and right ventricles.

Spectral and color-flow Doppler echocardiography are also helpful in assessing cardiac function in dogs with DCM.[130] Color-flow Doppler echocardiography permits identification of any valve leaks, and provides a rough estimation of the severity of valvular insufficiency. Doppler indices of systolic performance derived from aortic flow velocity profiles, such as peak acceleration rate and time to peak acceleration, are reduced in humans and dogs with DCM.[131, 132] These measures are particularly useful for evaluating and quantifying the effects of treatment. Such measures may be most useful in the context of dobutamine stress testing, wherein the goal is to identify dogs with subclinical myocardial dysfunction. Evaluation of spectral Doppler mitral inflow velocity profiles allows noninvasive assessment of diastolic function, which is otherwise quite difficult to accomplish. Preliminary studies in humans with DCM suggest that certain abnormalities of diastolic function, such as a prolonged relaxation time and increased early diastolic to atrial wave ratio (E/A), are associated with markedly reduced exercise tolerance and an adverse outcome (poor survival) in patients with DCM.[133]

DETECTION OF EARLY, SUBCLINICAL, OR "OCCULT" MYOCARDIAL DISEASE

Many investigators have worked diligently over the last decade to define the natural history of canine DCM, and some of the most thorough studies have been performed in Doberman pinschers. The two principal manifestations of Doberman cardiomyopathy are cardiac arrhythmias and progressive left ventricular dysfunction, just as the two principal causes of death related to DCM in this breed are sudden death and refractory congestive heart failure.[127, 134] Many studies have focused on defining the precise relationship between these phenomena over time, using echocardiography and electrocardiography. In this fashion, these investigators have begun to develop criteria useful for identifying those dogs that are likely, over the course of several years, to die suddenly or develop overt congestive heart failure.

Several groups of investigators have demonstrated that randomly selected and apparently healthy (asymptomatic) Doberman pinschers have reduced myocardial contractility compared with other breeds of dogs.[23, 124, 126, 135] Additionally, asymptomatic Doberman pinschers have been shown to manifest histologic evidence of myocardial disease that is typical of that found in dogs with congestive heart failure due to DCM.[125] Such findings indicate that Doberman pinschers have reduced myocardial reserve prior to the onset of heart failure, presumably as the result of some innate or acquired myocardial defect.[93–95]

In a recent study, echocardiographic evaluation of 192 asymptomatic Doberman pinschers demonstrated a mean fractional shortening (FS) of 20 percent; a mean left ventricular internal diastolic dimension (LVIDd) of 39.9 mm; and a mean left ventricular internal systolic dimension (LVIDs) of 31.9 mm.[26, 136] Twenty-seven of these 192 dogs (14 percent) also demonstrated at least one ventricular premature beat during a 3- to 6-minute rhythm strip or during the echocardiogram, and 4 percent demonstrated at least one supraventricular beat. In a subsequent study, 51 dogs were identified (from the original group of 192 just described) that showed no evidence of arrhythmia and no deterioration in ventricular function for at least 2 years following the initial evaluation.[137] In this group of 51 dogs, which might be considered representative of the "normal" Doberman pinscher population, the mean FS was 21 percent (range, 13 percent to 30 percent), the mean LVIDd was 39.1 mm (range, 32.7 to 45.2 mm), and the mean LVIDs was 31 mm (range, 25.7 to 37.9 mm).

Another prospective investigation followed the progress of 103 initially asymptomatic Dobermans.[126] Twenty-nine of 103 dogs (28.2 percent) developed signs of CHF or died of DCM during the 2.4-year-long follow-up period, including 13/15 dogs with LVIDd greater than 46 mm and 14/14 dogs with LVIDs greater than 38 mm on the initial examination. Of the 15 dogs in this study demonstrating at least one VPC during the initial examination, all were dead of DCM by the end of the study period, and 38 percent of these deaths were classified as sudden death.[126] After a follow-up period of 4.5 years, 44 of 103 dogs had either died suddenly (i.e., 24 dogs) or died from CHF (20 dogs). Nine other remaining dogs developed progressive myocardial dysfunction.[138] Based on these studies, criteria were proposed to identify those Doberman pinschers that are at substantial risk of developing overt DCM. These criteria included an LVIDd of greater than 46 mm or an LVIDs of greater than 38 mm. Working independently, Calvert and associates developed slightly different echocardiographic criteria for recognizing "occult" myocardial disease in asymptomatic Doberman pinschers.[22, 23] These criteria include FS less than 25 percent, LVIDd greater than 45 mm in dogs weighing less than 38 kg, LVIDd greater than 49 mm in dogs weighing more than 37 kg, E-point septal separation (EPSS) greater than 8 mm, and mean velocity of circumferential fiber shortening less than 1.5 circ/sec.

Ventricular arrhythmias also serve as a marker for "occult" myocardial disease in Doberman pinschers. Table 27–4 shows the Holter (ambulatory ECG) findings in 104 asymptomatic Doberman pinschers studied at the University of Georgia. Most (70 percent) asymptomatic Doberman pinschers less than 4 years of age did not demonstrate VPCs during a 24-hour Holter recording, whereas about half of all dogs 4 years of age and older had evidence of ventricular ectopy.

TABLE 27–4
Percentages of Overtly Healthy Doberman Pinschers with Normal Echocardiograms That Had Ventricular Premature Contractions (VPCs) on a 24-Hour Holter Recording

Age	Number of VPCs 0 (n = 55)	1–10 (n = 41)	11–50 (n = 10)	51–100 (n = 3)	>100 (n = 5)	P/T
<4 yr (n = 37)	70%	19%	3%	3%	5%	11%
4–6 yr (n = 47)	32%	47%	15%	4%	2%	21%
>6 yr (n = 30)	47%	40%	6.5%	0%	6.5%	13%

PT = at least one pair or triplet.

From Calvert CA: Long-term ambulatory electrocardiographic monitoring in the diagnosis of occult cardiomyopathy in Doberman pinschers. Proc Annual Meeting American College of Veterinary Internal Medicine, 1991, p. 691. Copyright 1991 by Clay A. Calvert.

Moreover, the number of dogs with VPCs increased with advancing age. Dogs with 50 to 100 VPCs almost always developed progressively more severe arrhythmias and echocardiographic abnormalities, although echocardiographic evaluation[127] was normal or equivocal on their initial evaluation. Dogs with over 100 VPCs and those with complex arrhythmias usually had at least subtle echocardiographic abnormalities and virtually always developed progressive cardiomyopathy. It is important to note that 12/19 (63 percent) of dogs that went on to develop DCM in a follow-up period of 3 to 8 years had less than 50 VPCs/24 hours on their initial examination. In a recent retrospective study, 54/54 Doberman pinschers that died suddenly or developed congestive heart failure had VPCs on a prior Holter recording (Table 27–5).[23] Nonsustained ventricular tachycardia (less than 30 seconds) had been documented by one or more Holter recordings in 12/14 (86 percent) dogs that died suddenly and in 15/40 (38 percent) dogs that developed heart failure. Sustained ventricular tachycardia (greater than 30 seconds) had been detected in 5/14 (36 percent) dogs that died suddenly and in 2/40 (5 percent) dogs that developed heart failure.

TABLE 27–5
Outcome Data from 103 Asymptomatic Doberman Pinschers After an Average Follow-Up Time of 2.4 Years

	Number *103*	Males *50*	Females *53*
Alive, no CHF	57	NR	NR
Alive with CHF	3	3	0
Alive, evidence of DCM[a]	17	NR	NR
Died of DCM	26	14	12
Died of sudden death[b]	10	5	5
Euthanized for CHF	14	7	7
Died of pump failure	2	2	0

[a]Criteria were LVID-S >38 mm, LVID-D >46 mm, or ventricular ectopy, where LVID-s and LVID-d = M-mode left ventricular internal dimension at end systole and end diastole, respectively.

[b]In five dogs, the first sign of DCM was sudden death. All dogs with at least one VPC on the initial examination died during the follow-up period due to DCM.

Fourteen dogs demonstrated LVID-s >38 mm on initial examination. All died of DCM or developed CHF due to DCM during the follow-up period. Fifteen dogs demonstrated an LVID-d >46 mm on initial examination; 13/15 died of DCM or developed CHF due to DCM during the follow-up period.

NR = not reported.

Data from O'Grady MR, Horne R. Outcome of 103 asymptomatic Doberman pinschers: incidence of dilated cardiomyopathy in a longitudinal study. Abstract. J Vet Intern Med 9:199, 1995.

From these and other studies, it can be concluded that Doberman cardiomyopathy is a chronic, slowly progressive, insidious disease with a protracted subclinical or occult stage. Furthermore, this disorder appears to evolve in many Doberman pinschers over a 2- to 4-year period prior to the onset of CHF. The rate of progression is somewhat dependent on the age at which an identifiable abnormality is first detected. Cardiomyopathy seems to develop more rapidly when identifiable abnormalities are detected in dogs less than 2 years of age and more slowly when abnormalities begin after 6 to 7 years of age. Doberman pinschers beyond 10 years of age with evidence of occult cardiomyopathy may die of nonrelated causes without the disease ever being suspected. Other factors contributing to the variability of disease progression have not yet been identified. Doberman pinschers with no arrhythmias and with a normal echocardiogram may develop abnormalities from developing DCM at any subsequent time. A threshold number of PVCs per hour (from Holter recordings) that predicts dogs destined to develop clinical DCM has not been determined, but those with greater than 100 VPCs/hour on a Holter recording should be highly suspect. Clearly, the detection of infrequent VPCs in an individual dog without other evidence of myocardial dysfunction does not establish a diagnosis of cardiomyopathy in Doberman pinschers or any other breed. Infrequent VPCs can appear from months to up to 1 year, or possibly longer, prior to the detection of echocardiographic changes, which, in turn usually occur well before the onset of clinical DCM. Depressed myocardial function is usually more obvious by the time frequent and complex rhythm disturbances are detected. Once myocardial contractility begins to decline, it may take from 5 months to over 2 years for overt heart failure to develop.

THERAPY

The ultimate treatment goal is to reverse the underlying disease process responsible for DCM before irreversible myocardial damage has occurred. Inasmuch as the underlying cause of DCM is unknown in most affected dogs, the goals of therapy are pragmatically reduced to identifying and reversing any precipitating cause(s) of heart failure, alleviating the clinical signs of heart failure, improving the quality of life, and reducing mortality. Therapeutic strategies continue to evolve in hopes of accomplishing these goals. Drugs currently used to treat dogs with DCM include digoxin and other more powerful inotropic drugs, diuretics, angiotensin-converting enzyme (ACE) inhibitors, vasodilators, and antiarrhythmic drugs, including beta-adrenergic receptor–blocking drugs and calcium antagonists. Treatment for heart failure must be tailored to the circumstances of the individual patient because no single drug or combination of drugs is effective in every dog at every stage of the disease. Further discussion of the principles of treatment and the drugs used to treat congestive heart failure may be found in chapter 12.

OPPORTUNITIES FOR A CURE. In two circumstances there is a distinct opportunity to resolve myocardial dysfunction: (1) when persistent or recurrent tachycardia causes heart failure, and (2) whenever taurine deficiency is identified. In both these circumstances, congestive heart failure must be treated using traditional medical therapy until myocardial dysfunction improves to normal or near-normal. Diuretics, ACE inhibitors, and digoxin may be needed for up to 6 months, because myocardial function improves only gradually following elimination of the precipitating abnormality. Dogs with sustained supraventricular tachycardia should be considered suspect for tachycardia-induced heart failure, particularly when the heart rate is more than 200 bpm and a predisposed breed, such as a Labrador retriever, is affected. An aggressive attempt should be made to abolish the arrhythmia or to reduce the heart rate. In many cases, there is no sure way to determine whether the arrhythmia was caused by or resulted from myocardial disease, but this dilemma should not deter a vigorous therapeutic effort. Taurine deficiency should be considered when DCM occurs in a cocker spaniel or golden retriever, as well as in atypical breeds or dogs eating unusual diets. Taurine supplementation, 250 mg bid, should be instituted whenever plasma or blood taurine concentrations are reduced (see chapter 32). Taurine supplementation should be initiated in cocker spaniels and golden retrievers even if taurine deficiency cannot be immediately confirmed.

TREATMENT OF ACUTE AND SEVERE CHF. Life-threatening pulmonary edema caused by DCM requires particularly aggressive therapy. Pulmonary edema is most effectively treated using IV furosemide in combination with sodium nitroprusside. Nitroprusside is a direct, ultrashort-acting, and extremely potent vasodilator that must be given by constant IV infusion. Beneficial hemodynamic effects of nitroprusside, documented in dogs with spontaneous CHF due to DCM, include increased cardiac output and decreased pulmonary capillary wedge pressures.[139] Sodium nitroprusside should be infused initially at a rate of 2.5 μg/kg/min. The rate of infusion can be increased incrementally until the patient has stabilized or until mean systemic arterial pressure falls below 70 mmHg. Infusion rates greater than 10 μg/kg/min are rarely needed. Furosemide, administered at 6 to 8 mg/kg IV and repeated every 4 hours for the first 12 hours, rapidly and effectively reduces plasma volume in dogs with fulminant pulmonary edema. An alternative regimen for furosemide administration is to administer 2 to 4 mg/kg IV every hour until the respiratory rate is less than 30 breaths per minute, then continue IV furosemide at 4 mg/kg every 6 hours. Constant-rate infusion of furosemide, administered after an initial IV bolus, may produce the most vigorous diuresis.[139]

Dobutamine, a $beta_1$-receptor agonist and potent positive inotrope, is also useful for treating dogs with profound myocardial failure. Dobutamine must be administered by constant-rate IV infusion, and it should not be mixed with sodium nitroprusside. Dobutamine is initially administered at an infusion rate of between 2.5 and 5.0 μg/kg/min. The infusion rate is increased by increments of 2.5 μg/kg/min every 2 hours until the heart rate increases excessively, ventricular ectopy increases by 20 percent, or a maximum infusion rate of 15 μg/kg/min is attained. Tolerance to dobutamine can develop within 24 to 48 hours after the onset of therapy.[140] Fortunately, most dogs can be weaned off IV drugs and onto oral drugs within 48 hours of initiating treatment. Dobutamine is usually the first drug to be discontinued. In anticipation of this event, oral digoxin should be initiated early. Oral diuretics, vasodilators, and ACE inhibitors are started when IV furosemide and nitroprusside are discontinued. Two phosphodiesterase III (PDE3) inhibitors, amrinone and milrinone, are approved for short-term IV therapy of heart failure in humans. Both drugs are sometimes referred to as "inodilators" because they are more potent inotropes than digoxin and possess substantial vasodilating properties. These drugs may not be as effective as $beta_1$-receptor agonists in the treatment of severe heart failure due to decreased gene expression and activity of the milrinone-sensitive cAMP phosphodiesterase.[141] Although oral milrinone has been used with some success to treat dogs with DCM, no studies have been published using the IV formulations.

Serious cardiac arrhythmias requiring treatment are often identified in patients with acutely decompen-

sated DCM (see chapters 17 and 18). The heart rate is often greater than 200 bpm in dogs with atrial tachycardia, atrial fibrillation, or atrial flutter. The occurrence of these arrhythmias in a dog with acute, decompensated heart failure warrants the use of IV digoxin. Alternatively, a calcium channel blocker, such as diltiazem, can often be used effectively to terminate the arrhythmia or to reduce the heart rate. Intravenous beta-blocking agents generally should be avoided in the setting of profound, acute heart failure. Ventricular arrhythmias are also treated if they are adversely affecting hemodynamic performance. Intravenous lidocaine or procainamide is a suitable choice for the short-term management of ventricular arrhythmia in this setting. Intravenous lidocaine is given at an initial dose of 2 mg/kg IV. If there is no response, another 2 mg/kg dose is administered. If these doses are effective, a constant-rate infusion of lidocaine should be started. Procainamide can be given if lidocaine is not effective, but it has a more profound myocardial depressant effect. Intravenous amiodarone may also be useful in dogs with severe ventricular arrhythmias, but we have no experience with this approach. In many dogs with DCM, ventricular ectopy declines with resolution of pulmonary edema, allowing discontinuation of parenteral antiarrhythmic therapy.

TREATMENT OF CHRONIC HEART FAILURE. Chronic maintenance therapy for dogs with CHF due to DCM consists of (1) sufficient furosemide to optimize venous pressure and alleviate congestion, (2) an ACE inhibitor to improve the quality of life and to decrease mortality, and (3) digoxin to control heart rate and improve exercise capacity. A low-sodium diet and exercise restriction are also important. High doses of furosemide are used initially to stimulate excretion of retained sodium and water. Thereafter, the dose of furosemide should be reduced to a level that controls congestive signs without causing excessive volume contraction. Diuretics are not benign drugs in that they activate the sympathetic and renin-angiotensin-aldosterone systems, and they promote potassium and magnesium loss, thereby favoring the development of cardiac arrhythmia. The lowest diuretic dose that controls congestive signs should be used. In dogs with refractory congestive signs, the addition of a second and rarely a third diuretic is sometimes required. In this circumstance, we prefer to add spironolactone in combination with a thiazide diuretic (see chapter 12).

Effective inhibition of ACE represents the cornerstone of modern CHF therapy. ACE inhibitors offer the best opportunity to extend survival and reduce the morbidity that accompanies congestive heart failure associated with DCM.[142–145] Of the many ACE inhibitors available for use, enalapril, lisinopril, benazepril, quinapril, and ramipril have been studied in dogs with naturally occurring heart failure.[146–151] Enalapril was the first ACE inhibitor approved in the United States and Europe for treatment of CHF in dogs. The Cooperative Veterinary Enalapril (COVE) study group reported that enalapril, used in combination with digoxin and furosemide, significantly reduces the clinical signs of heart failure and improves exercise tolerance in dogs with CHF from DCM.[14] The Invasive Multicenter Prospective Veterinary Enalapril (IMPROVE) study group reported that enalapril, dosed at 0.5 mg/kg q12h, produces a significant decline in pulmonary capillary wedge pressure (PCWP) in dogs with heart failure caused by DCM.[147] Controlled studies have also shown that enalapril significantly increases the time to development of refractory heart failure or death in dogs with DCM.[14] The average estimated survival/time to treatment failure for dogs with DCM that received digoxin, furosemide, and placebo was 58 days, whereas the dogs with DCM that received digoxin, furosemide, and enalapril was 157 days.[14] Other ACE inhibitors, such as lisinopril, are likely to be as effective when appropriate doses are used. Combination therapy with an arterial vasodilator (hydralazine or amlodipine) and a nitrate is an acceptable alternative for patients that do not tolerate ACE inhibitors.[143, 152] These vasodilators may also be useful adjunct therapy for dogs with persistent signs of heart failure following treatment with digoxin, furosemide, and ACE inhibitors.

Digoxin is indicated in most dogs with DCM and signs of heart failure.[7, 153] Although its effects are variable and difficult to quantify, digoxin has been shown to exert a significant positive inotropic effect in some dogs with DCM.[154] Moreover, most dogs exhibit a beneficial clinical response. In several large clinical trials in humans, digoxin therapy reduced symptoms, improved exercise capacity, and decreased the risk of clinical deterioration of heart failure.[155–157] The effect of digoxin on mortality and morbidity in a study of 6800 human patients with heart failure and reduced ejection fraction was reported in 1997.[158] This landmark double-blind, placebo-controlled study concluded that digoxin reduces the rate of hospitalization and the rate for worsening heart failure. Digoxin had a neutral effect on mortality (survival), distinguishing it from other more potent positive inotropes that increase mortality.[158] Studies of this magnitude are not likely to be duplicated in dogs. Digoxin reduces activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system.[123, 159] Digoxin is also moderately effective for slowing the ventricular rate in dogs with atrial fibrillation.[160] The dose of digoxin should be adjusted, by periodic monitoring of digoxin serum concentration, to maintain the serum digoxin level between 0.9 and 1.5 ng/ml.

TREATMENT OF ARRHYTHMIAS. Atrial fibrillation and ventricular tachycardia are the most common rhythm disorders requiring treatment in dogs with DCM. The

detrimental hemodynamic effects of atrial fibrillation include reduced cardiac output, by as much as 25 percent, and a substantial increase in filling pressures, thereby substantially worsening congestive signs. These changes are due to the loss of synchronized atrial contractions and to reduced ventricular filling resulting from an excessively fast heart rate. It is not possible, with existing approaches, to re-establish and maintain sinus rhythm in most dogs with atrial fibrillation developing in association with DCM. The aim of treatment is to reduce and maintain heart rate between 140 and 160 bpm. If the situation is not urgent, 5 to 7 days can be allowed for digoxin to achieve a steady-state concentration; otherwise, more rapid digitalization should be accomplished.

An adequate reduction in heart rate may not be accomplished with digoxin alone. Combination therapy using digoxin together with either a beta-adrenergic receptor blocking drug or a calcium channel blocker is often required to optimize heart rate. Calcium channel blockers are reported to be the most effective agents to reduce the heart rate,[161] but chronic treatment with a beta-blocker may have a more beneficial effect on myocardial function in patients with DCM.[162, 163] Diltiazem, dosed at 1.0 to 1.5 mg/kg q8h, often gives excellent heart rate control. If beta-blockers are used, a low dose is used initially, and the dose is then gradually raised by 25 percent to 50 percent each week to achieve the desired effect. Atenolol is started at 12.5 mg q24h in large breed dogs, e.g., a 30-kg Doberman pinscher. Alternatively, metoprolol can be initiated at 5.0 mg q12h. Some dogs are very sensitive to beta-blockers such that a trivial dose results in a marked reduction in heart rate and worsening heart failure.

The role of antiarrhythmic therapy for ventricular ectopia in dogs with DCM is uncertain. Studies in human patients suggest that most antiarrhythmic agents, likely all the class I agents, increase the mortality of patients who are not symptomatic as a result of their arrhythmias.[164–166] In most human patients with structural heart disease, ventricular premature beats, even if they are very numerous, vary in morphology or occur in a bigeminal pattern or as couplets, are not an indication for treatment unless they are causing debilitating symptoms.[167] Antiarrhythmic therapy is generally reserved for those patients who are symptomatic from their arrhythmia. Sustained ventricular tachycardia or bursts of ventricular tachycardia with instantaneous rates of greater than 200 bpm usually cause substantial disability and should be treated.

The choice of antiarrhythmic therapy in dogs with DCM is controversial and somewhat arbitrary in that no controlled studies have been performed to evaluate the safety or efficacy of any antiarrhythmic drug. Of the many possible approaches, a few can be recommended. Sustained-release procainamide can be administered at 20 mg/kg q8h, and the dose can be increased to 30 mg/kg q8h if needed and adequate blood levels of procainamide have not been achieved. Continued ventricular ectopy may require the addition of a beta-blocker such as atenolol or metoprolol. As in dogs with atrial fibrillation, low doses are used initially and the dose is gradually increased to effect. Harpster reported preliminary data suggesting that survival of boxer dogs with DCM may be improved with use of procainamide, usually in combination with propranolol.[25] Calvert and colleagues reported that tocainide, administered at 15 to 25 mg/kg q8h, was effective in suppressing ventricular arrhythmias in 80 percent to 90 percent of Doberman pinschers with DCM, but they did not comment on survival.[168] Anorexia and gastrointestinal disturbances occurred in 35 percent of treated dogs. Moreover, 58 percent of dogs treated longer than 4 months experienced serious side effects, including progressive corneal dystrophy and possibly renal dysfunction.

Sotalol and other class III antiarrhythmic drugs may also be useful for treating ventricular arrhythmia in dogs with DCM, but there are no canine studies regarding the efficacy or safety of these agents. Personal observation suggests that sotalol is sometimes effective when other treatments fail. Sotalol is initially dosed at 20 mg/dog q12h in large breed dogs, and the dose is then titrated upward. Evaluating the response to antiarrhythmic drugs is difficult. Longevity trials are required to determine effect on survival, and no such studies have yet been performed in dogs. Repeated ambulatory ECG recordings of at least 6 hours are needed to demonstrate that the targeted arrhythmia is being effectively suppressed.[124] If this is not feasible, repeated 10-minute ECG recordings should be performed in preference to 1- or 2-minute rhythm strips. The goal of treatment is to abolish bouts of sustained or nonsustained ventricular tachycardia, not to completely extinguish every premature beat.

NOVEL TREATMENTS OF UNCERTAIN BENEFIT. A number of promising drugs designed for the treatment of DCM and CHF are being evaluated in human clinical trials.[169] Currently, there is particular interest in beta-adrenergic receptor blocking drugs. Beta-blockers reduce plasma norepinephrine concentrations, increase beta-receptor density, up-regulate the previously down-regulated beta-adrenergic receptors, and, paradoxically, increase the contractility of the failing heart (see chapter 12).[170, 171] Beta-blockers also suppress certain arrhythmias, reduce myocardial oxygen demand, and improve the efficiency of myocardial energy utilization, resulting in improved hemodynamics and reduction in clinical symptoms in some human patients with DCM.[172–176] Bisoprolol, metoprolol, and carvedilol are among a small group of beta-blockers that have been intensively studied in patients with DCM.[177–179] Bisopro-

lol and metoprolol are both $beta_1$-receptor blocking drugs, whereas carvedilol exhibits both $alpha_1$- and $beta_1$-receptor blocking activity.

Carvedilol and bisoprolol, but not metoprolol, have been shown to reduce mortality in patients with DCM.[177–179] Although these results are encouraging, many heart failure patients do not tolerate beta-blocker drugs even at very low doses. A substantial percentage of patients experience rapid cardiac decompensation and worsening congestive signs, and some die as a result of this treatment. Efficacy has not yet been demonstrated in dogs with DCM, and further studies are needed before the widespread use of beta-blockers can be recommended (see chapter 12).

After considering the potential benefits of beta-blockers, it is ironic to note that some patients with DCM and profound myocardial failure continue to be successfully treated with intermittent infusion of the $beta_1$-receptor agonist dobutamine.[180] Such therapy is advocated as a bridge to heart transplantation in human patients. Some patients improve remarkably and can go for months between infusions. Perpetual hope prompts the continued search for a potent, safe, and orally absorbed positive inotropic drug. Most potent positive inotropes reduce survival times when they are administered chronically. Vesnarinone and pimobendan are phosphodiesterase III inhibiting drugs possessing attributes that might improve their safety and efficacy when used chronically in patients with CHF.[181, 182] Vesnarinone enhances sodium influx into myocardial cells, thereby increasing calcium delivery to the myofilaments, whereas pimobendan appears to sensitize the contractile apparatus to intracellular calcium. Given the adverse effects of other phosphodiesterase inhibitors on survival, the future of this entire class of drugs is not particularly optimistic.

A number of surgical remedies have been devised to rescue patients that fail to respond to medical treatment. Such recourse is not an affordable or pragmatic option for most owners, and it is unlikely that this approach will play a substantive role in the management of canine DCM. The most successful surgical remedy for DCM is a heart transplant.[183] Other surgical remedies are much less successful and are generally performed only when a heart transplant cannot be performed. Cardiomyoplasty involves covering both ventricles with an envelope of skeletal muscle, usually the latissimus dorsi, and pacing this repositioned muscle to support the heart.[184] This procedure has been performed in dogs.[185] An alternative surgical method of supporting the circulation consists of placing a skeletal muscle wrap around a small segment of the abdominal aorta and pacing this muscle to mimic the effect of intra-aortic balloon counterpulsation.[186] Dual-chambered cardiac pacing with a short PR interval has been shown to improve cardiac output and exercise capacity in some human patients with DCM.[187] Clinical benefit is dependent on the pattern of left ventricular activation, and no hemodynamic advantage is afforded by this modality in most dogs with DCM.[188]

PROGNOSIS

Owners should be advised that unless an underlying cause for DCM can be identified and reversed, all cases of DCM are terminal. Owners should also be advised that survival times, even with optimal therapy, are highly variable from one patient to the next. Some very ill dogs improve to a remarkable degree with treatment and live a comfortable existence for many months or even years. Other dogs do not survive the initial 48 hours of hospitalization. It is simply not possible to predict how well an individual dog with DCM will respond to treatment or how long that animal will live. In dogs with severe heart failure at the time of presentation, a prudent approach is to recommend medical therapy and evaluate the initial response before rendering a tentative prognosis.[189]

The devastating nature of DCM is most obvious in Doberman pinschers. O'Grady and Horne reported that of 103 Doberman pinschers that were initially asymptomatic, 26 went on to die of DCM during an average follow-up time of 28 months[126] (see Table 27–5). Regarding these 26 deaths, 14 owners declined further therapy for the pulmonary edema and the dogs were euthanized, 2 dogs died of progressive pump failure, and 10 dogs died suddenly. In this small follow-up group, 38 percent of all cardiac deaths were due to sudden death and 62 percent died as a result of heart failure. After an average follow-up time of 4.5 years, 24 of the dogs had died suddenly, 20 dogs had been euthanized because of CHF, and 11 dogs had developed progressive myocardial dysfunction and were either alive or had died from noncardiac causes (Table 27–6).[138] Overall, 63.2 percent of 103 initially asymptomatic Doberman pinschers (78 percent of the males, and 50 percent of the females) died suddenly, developed CHF, or showed echocardiographic deterioration during the study. Calvert and associates reported that of 57 Doberman pinschers dying from DCM, 40 (70 percent) died after developing congestive heart failure, 14 (25 percent) died suddenly, and 3/57 (5 percent) died of unrelated causes.[23] Sudden death in Doberman pinschers usually occurs during or immediately following exertion but may occur during sleep. Sudden death is frequently the first evidence of occult DCM, and many Doberman pinschers that collapse due to ventricular tachycardia die during the first episode. Survivors of one episode of collapse often die during a second episode 1 day to many months later. Some lines of Dobermans show a high incidence of sudden death.

Other recent studies have also addressed the issue of survival in dogs with DCM.[15, 18, 22] Most of the studies

TABLE 27–6
Outcome Data From 103 Asymptomatic Doberman Pinschers After an Average Follow-Up Time of 4.5 Years

	Number *103*	Males *50*	Females *53*
Alive, no CHF	32	9	23
Alive, evidence of DCM†	9	5	4
Died of DCM	44	25	19
Died of sudden death*	24	13	11
Euthanized for CHF	20	12	8
Died of unknown causes	1	NR	NR
CHF, died from other causes	2	2	
Died from other causes	12	NR	NR
Lost to follow-up	3	NR	NR

*In 15 dogs, the first historical sign of DCM was sudden death; 9 dogs died suddenly after the onset of CHF.
†Criteria were LVIDs >42 mm, LVIDd >49 mm, or ventricular ectopy, where LVIDs and LVIDd = M-mode left ventricular internal dimension at end-systole and end-diastole, respectively.
NR = not reported.
From O'Grady M, Horne R: Prevalence of dilated cardiomyopthy in Doberman pinschers: a 4.5 year follow-up. Abstract. J Vet Intern Med 12:199, 1998.

were retrospective studies, and most included a large percentage of dogs that were euthanized. It is important to note that therapy was not standardized in most of these studies. None included an aggressive protocol for treating acute CHF. Dobutamine and nitroprusside were rarely if ever used, and most of the dogs studied were not treated with an ACE inhibitor. For these reasons, the data reported are more a reflection of the natural history of DCM than an indication of what can be accomplished with treatment.

A Swedish study reported survival data from 189 dogs (including 38 breeds) with DCM.[15] Most dogs (92 percent) died or were euthanized for reasons related to heart disease. Euthanasia was performed in 27 cases at the time of presentation. Eighteen dogs (10 percent) died suddenly, and 128 dogs (74 percent) were eventually euthanized for treatment failure (CHF). The survival rate was 17.5 percent at 1 year and 7.5 percent at 2 years (Fig. 27–7). Three independent predictors of survival were identified: age—dogs less than 5 years old had shorter survival times; (2) dyspnea at the time of presentation; and (3) ascites. Treatment was not standardized in this retrospective study. No dog received dobutamine or a nitrate, and only 9 percent of the dogs were treated with an ACE inhibitor.

Monnet and colleagues performed Kaplan Meier survival analysis in a diverse breed population of 37 dogs with DCM, reporting that the 50 percent probability of survival occurred at 2.3 months.[18] Probability of survival at 1 year was 37.5 percent, and at 2 years was 28 percent. Four dogs died from noncardiac-related causes. The prevalence of sudden death was not reported. Dogs surviving more than 7 months appeared to have a good probability of becoming long-term survivors. Treatment was not standardized in this retrospective study. No dog received dobutamine or a nitrate, and only 10/37 dogs (27 percent) were treated with ACE inhibitors. Pulmonary edema and pleural effusion were identified as independent prognostic indicators.

Calvert and colleagues studied the survival of 66 Doberman pinschers that presented with signs of CHF of no more than 2 weeks' duration.[22] Sudden death occurred in 20 percent of the dogs. Mean and median survival times were 9.65 weeks and 6.5 weeks, respectively. Dogs with atrial fibrillation or bilateral CHF at presentation had shorter survival times than dogs that did not (Fig. 27–8). Treatment was not standardized in this retrospective study. None of the 66 dogs presenting with pulmonary edema received nitroprusside; only two dogs were treated with dobutamine, and only 25/66 dogs (38 percent) were treated with an ACE inhibitor.

In the only prospective study in which treatment was standardized and controlled, the average estimated survival time (time to treatment failure) was 158 days when the dogs were treated with digoxin, furosemide, and enalapril, compared with 58 days when they were treated only with digoxin and furosemide.[14] Subgroup analysis revealed that DCM in the Doberman pinscher carries a worse prognosis than in other breeds with DCM. The average estimated survival time for Doberman pinschers on enalapril was 80 days compared with 260 days for all other breeds combined.[14] Another retrospective study also showed that survival is shorter in Doberman pinschers with DCM than in other breeds.[190] Variables of prognostic value in human pa-

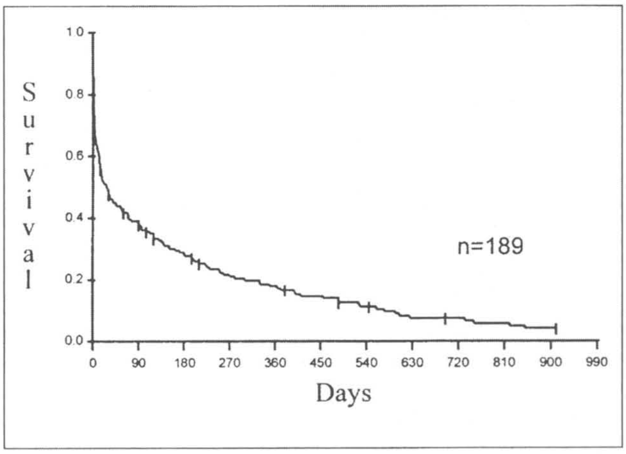


FIGURE 27–7

Survival curve for 189 dogs with dilated cardiomyopathy. Survival rate at 1 year after initial diagnosis was 17.5 percent and at 2 years was 7.5 percent. Treatment was not standardized in this retrospective study. No dog received dobutamine or a nitrate, and only 9 percent of the dogs were treated with an ACE inhibitor. (From Tidholm A, Svensson H, Sylvén C. Survival and prognostic factors in 189 dogs with dilated cardiomyopathy. J Am Anim Hosp Assoc 33:364, 1997.)

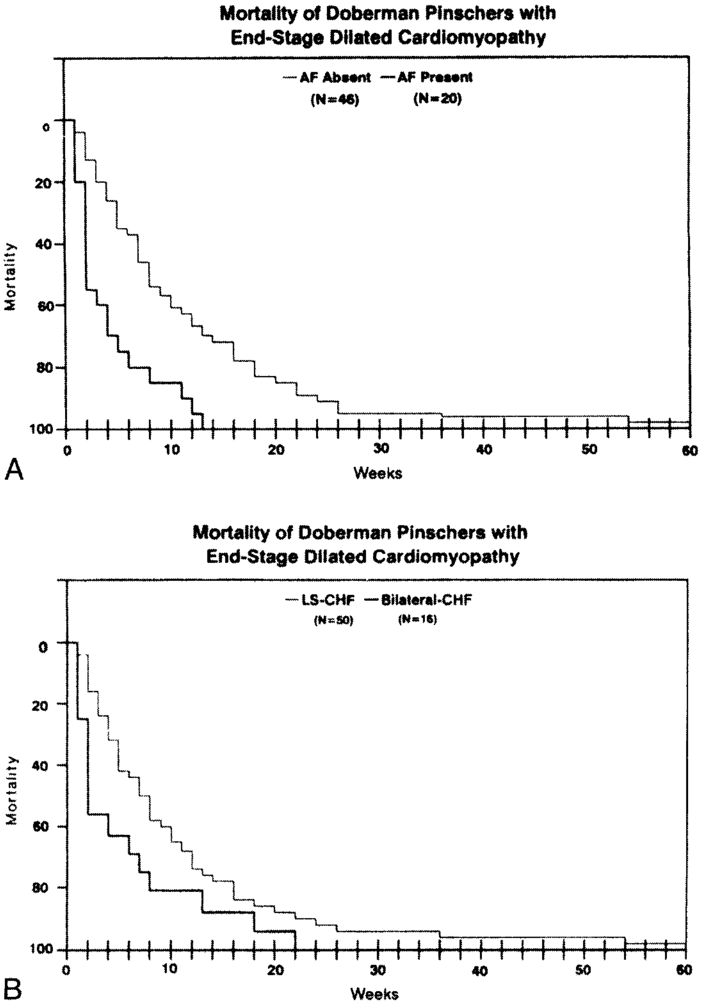


FIGURE 27-8

(A) Survival curves comparing the influence of atrial fibrillation (AF) versus sinus rhythm (SR) on survival. Atrial fibrillation was associated with significantly shorter survival time ($P < .001$). (B) Survival curves comparing the influence on survival of bilateral congestive heart failure (CHF) versus left-sided CHF. The presence of bilateral CHF at the time of presentation was associated with significantly shorter survival time ($P < .05$). (From Calvert CA, Pickus CW, Jacobs GJ, et al. Signalment, survival and prognostic factors in Doberman pinschers with end-stage cardiomyopathy. J Vet Intern Med 11:323, 1997.)

tients with DCM include degree of left ventricular dysfunction (ejection fraction), presence or severity of hyponatremia, degree of left ventricular enlargement, presence or degree of mitral valve insufficiency, presence or severity of ventricular arrhythmias, presence of atrial fibrillation, and plasma norepinephrine, atrial natriuretic peptide (ANP), and brain natriuretic peptide (BNP) concentrations.[191] Larger and more sophisticated prospective studies are required before the effect of these variables can be accurately assessed in dogs with DCM.

HYPERTROPHIC CARDIOMYOPATHY IN DOGS

Hypertrophic cardiomyopathy (HCM) is pragmatically defined as inappropriate myocardial hypertrophy of a nondilated left ventricle, occurring in the absence of an identifiable stimulus for the hypertrophy.[1, 6] As currently defined, HCM probably encompasses a number of different disease processes that share certain functional and morphologic features. A diagnosis of HCM implies that the patient is free of valvular or fixed subaortic stenosis, severe systemic hypertension, or any one of the many metabolic disorders or endocrinopathies capable of inducing left ventricular hypertrophy. Human patients with HCM are subclassified into obstructive and nonobstructive categories.[1, 6] About 25 percent of people with HCM demonstrate dynamic obstruction to left ventricular outflow, characterized, in most cases, by systolic apposition of the mitral valve with the interventricular septum. In the older literature, this variant of HCM was often referred to as idiopathic hypertrophic subaortic stenosis (IHSS) and muscular subaortic stenosis. The development of dynamic left ventricular outflow tract (LVOT) obstruction appears to be predicated on the pattern of left ventricular hypertrophy and certain morphologic changes in the mitral valve apparatus.

Hypertrophic cardiomyopathy is an infrequently identified cause of heart disease in dogs.[7, 192-197] The majority of identified dogs have been males, and most have been diagnosed prior to 3 years of age, suggesting that this is a congenital disorder.[7] Breeding trials have shown that HCM is inherited in pointer dogs.[198] Hyper-

trophic cardiomyopathy has been identified in many different breeds, including German shepherds, Rottweilers, Dalmatians, cocker spaniels, Brittany spaniels, Shih Tzus, Doberman pinschers, Airedales, poodles, Great Danes, bulldogs, Boston terriers, Walker hounds, boxers, German short-haired pointers, Weimaraners, miniature schnauzers, Rhodesian ridgebacks, and golden retrievers.[7, 192–197] Hypertrophic cardiomyopathy in dogs differs from the human disorder in several important aspects. Two common (characteristic) features of HCM in people—disproportionate hypertrophy of the septum and myocardial fiber disarray—are observed infrequently in dogs with HCM.[198–200] Inasmuch as the great majority of affected dogs evidence dynamic LVOT obstruction without these defining morphologic criteria, it is possible that myocardial hypertrophy, at least in some dogs, is not the primary abnormality but is simply a consequence of dynamic outflow tract obstruction.[201, 202] It is interesting that systolic anterior motion of the mitral valve resulting in dynamic LVOT obstruction has been created experimentally in dogs simply by displacing the anterior papillary muscle.[203]

PATHOLOGY

A number of diverse patterns of left ventricular hypertrophy have been identified in humans and cats with HCM (see chapter 28).[199] The majority of people with HCM show disproportionate (asymmetric) hypertrophy of the interventricular septum, wherein septal thickness greatly exceeds the thickness of the left ventricular free wall. In fact, asymmetric septal hypertrophy (ASH) was once the only recognized form of HCM in humans. A minority of human patients have symmetric concentric LV hypertrophy with equal involvement of the interventricular septum and free wall. Other less frequent but recurring patterns of hypertrophy include focal hypertrophy of the posterior portion of the septum, the posterobasal free wall, or the apical region of the LV.[1, 199] The left ventricular cavity is usually reduced in volume, and the left atrium is usually dilated and hypertrophied. The right ventricle is also frequently hypertrophied, but this is not a prominent feature of the disease.

One of the most prominent pathologic features of HCM in humans is disarray or malalignment of the myofibers in the hypertrophied septum or LV free wall, and it is often cited as the most consistent feature of HCM in humans.[1, 4, 6, 199, 200, 204] Myocardial fiber disarray is considered by some investigators to be the most consistent finding in people with HCM. Fiber disarray has been observed in other forms of cardiac disease, but the amount of disarray is much more extensive in patients with HCM.[199] The left ventricular outflow tract is narrowed in patients with the obstructive form of HCM. In these patients, a fibrous endocardial plaque is present on the interventricular septum directly opposite a thickened anterior mitral valve leaflet. These lesions are impact lesions resulting from abnormal systolic anterior motion (SAM) of the mitral valve.[4, 7] A variety of mitral valve malformations, including elongation of the anterior leaflet, have been described in patients with HCM, particularly in the obstructive form of this disorder, suggesting that HCM is not simply a disease of the myocardium.[203, 205, 206]

In most dogs with HCM, left ventricular hypertrophy is symmetric; that is, the septum and LV free wall are hypertrophied to the same extent. When asymmetric septal hypertrophy is identified, it is not as dramatic as in human patients. Pathologic evidence of dynamic LVOT obstruction is observed in most of the dogs with HCM, while a small minority manifest no sign of obstruction. In young dogs, the impact lesion on the interventricular septum is often subtle, appearing as a discrete but subtle opaque area. In older dogs, a thickened plaque of connective tissue is visible just opposite an obviously thickened anterior mitral valve leaflet (Fig. 27–9). The mitral valve apparatus is abnormal in many dogs with HCM. In some dogs, the anterior mitral valve leaflet is obviously elongated or redundant valve tissue protrudes into the outflow tract. In other dogs, the papillary muscles are abnormally oriented, tending to displace the mitral valve leaflet toward the outflow tract. In some dogs, a discrete muscular ridge is observed coursing through the long axis of the LVOT.

In most affected dogs (90 percent), histology shows hypertrophied myocardial fibers that are normally oriented. Myocardial fiber disarray has been reported in only 2 dogs with HCM.[192, 193, 199, 200] Abnormalities of the intramural coronary arteries can be found in all affected dogs, particularly in the LV wall, interventricular septum, and papillary muscles (Fig. 27–9). Observed changes include intimal hyperplasia, with hypertrophy and hyalin degeneration of the smooth muscle in the media. Similar changes have been described in the intramural coronary arteries of humans with HCM and dogs with subvalvular aortic stenosis (SAS).[1, 6, 199, 207] Associated with these vascular lesions are focal areas of myocardial necrosis, fibrosis, and dystrophic calcification. Such changes are most obvious in the papillary muscles and in subendocardial regions of the interventricular septum and LV wall.

The relationship between canine HCM, fixed SAS, and mitral valve dysplasia is uncertain.[201, 208] Approximately one-half of the HCM cases reported in dogs involved breeds (Rottweiler, German shepherd, and boxer dogs) predisposed to congenital fixed subvalvular aortic stenosis. Subvalvular aortic stenosis in dogs was described in early reports as a discrete, fibrous obstruction encircling the LVOT below the aortic valve. Recent observations suggest that the morphology of SAS is more diverse.[191, 209] In some dogs with

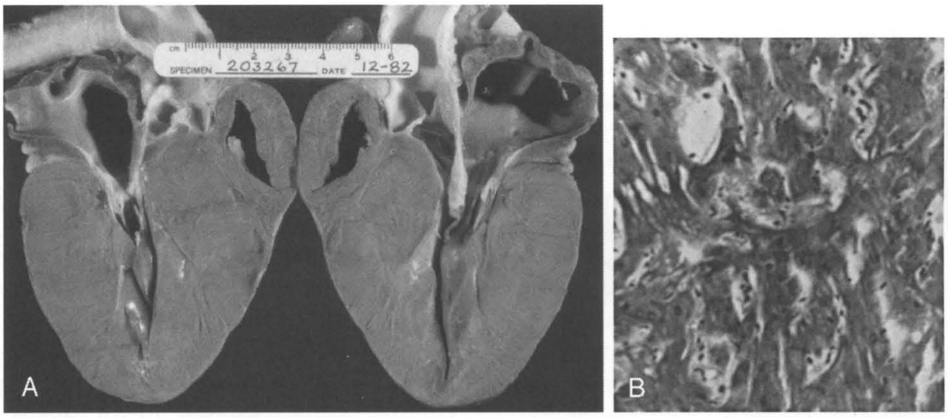


FIGURE 27–9

(A) Gross pathology of the obstructive form of hypertrophic cardiomyopathy in a Rottweiler shows marked concentric left ventricular hypertrophy, a small left ventricular cavity, and a fibrous plaque on the septal endocardium opposite a thickened and fibrotic mitral valve. (B) Disorganized myofibers are shown in a section of myocardium from the septum of another dog with HCM. H&E stain × 100. (From Liu S-K, et al. Canine hypertrophic cardiomyopathy. J Am Vet Med Assoc 174:708, 1979.)

SAS, the obstructing subvalvular lesion is a less distinct fibromuscular bulge occupying the base of the interventricular septum. Some dogs with SAS have concurrent dynamic LVOT obstruction, and some have a muscular ridge on the interventricular septum adjacent to the anterior papillary muscle coursing through the long axis of the LVOT, similar in appearance to that observed in dogs with HCM. Further complicating the distinction between SAS and HCM is the observation that mitral valve dysplasia commonly coexists with SAS in dogs (see chapter 24). Consideration must be given to the possibility that some cases of suspected HCM in dogs represent a muscular variant of congenital SAS or an unusual consequence of mitral valve dysplasia.

PATHOGENESIS/ETIOLOGY

The cause of HCM in dogs is uncertain, although a heritable basis is suspected. Breeding studies performed by one of the authors (Sisson) demonstrated the heritability of dynamic LVOT obstruction and LV hypertrophy in pointer dogs.[198] A polygenic or autosomal recessive pattern of inheritance best explained the observed pattern of occurrence in this study. Fifty percent to 60 percent of human HCM cases are familial, usually showing autosomal dominant inheritance, while the remainder are sporadic.[1, 6, 209] Genetic heterogeneity has been demonstrated; and linkage studies and candidate-gene approaches have demonstrated that affected patients may have mutations in one of seven different genes: cardiac beta-myosin heavy chain (cbeta MHC), cardiac troponin T (cTnT), alpha-tropomyosin (alpha TM), cardiac myosin binding protein C (cMBPC), ventricular myosin essential light chain (vMLC1), ventricular myosin regulatory light chain (vMLC2) genes, and cardiac troponin I (cTnI).[210] A defect in mitochondrial DNA has also been identified in several members of a family affected by a maternally inherited form of hypertrophic cardiomyopathy.[211]

The mechanism(s) by which these genetic abnormalities cause hypertrophy is unknown. Some studies suggest that there is an increase in the number of calcium channels, mediating abnormal calcium fluxes and producing, by some unknown mechanism, hypertrophy and fiber disarray.[6] Other possible causes of HCM include (1) abnormal sympathetic activity; (2) abnormally thickened intramural coronary arteries that do not dilate normally and lead to myocardial ischemia, with resultant fibrosis and abnormal compensatory hypertrophy; (3) abnormalities of the microcirculation, resulting in myocardial ischemia and depletion of the energy stores essential for the sequestration of calcium during diastole, causing increased diastolic stiffness; and (4) structural abnormalities, including a catenoid configuration of the septum, that lead to myocardial cell hypertrophy and disarray.[6]

PATHOPHYSIOLOGY

Two principal functional disturbances occur in patients with HCM: impaired diastolic filling and dynamic LVOT obstruction. Altered diastolic filling is the most pervasive hemodynamic change in human patients because it is abnormal in patients with and without LVOT obstruction.[1, 6] Diastolic dysfunction results from impaired relaxation in early diastole and from reduced ventricular compliance. The reduced rate and uniformity of ventricular relaxation in early diastole are thought to be caused by abnormal myocardial calcium kinetics, which result in increased concentrations of intracellular calcium.[212] Reduced ventricular

compliance results from the combined influences of reduced chamber size, increased wall thickness, and intrinsic changes in wall stiffness.[1, 6, 212] In human patients with HCM, the severity of diastolic impairment does not correlate with the extent or distribution of hypertrophy or with the presence or severity of LVOT obstruction.[6] The consequences of diastolic dysfunction include an impaired ability to increase cardiac output during stress or exercise, as well as a propensity to develop pulmonary congestion and edema due to increased left atrial and pulmonary venous pressures. Any increase in heart rate exacerbates the severity of diastolic dysfunction.

The phenomenon of left ventricular outflow tract obstruction is well documented in humans, dogs, and cats with HCM (see chapter 28). Dynamic obstruction typically develops in midsystole, after most of the stroke volume has been ejected from the left ventricle (see Fig. 24–21*A*).[213–215] The obstruction results from systolic apposition of the mitral valve to the interventricular septum. Systolic anterior motion (SAM) of the mitral valve develops when the leaflets are drawn into the outflow tract by Venturi forces generated by rapid blood flow through an already narrowed LVOT. The mitral leaflets may also be pulled into the outflow tract by malaligned papillary muscles or pushed toward the septum by the ejected blood. Regardless of the precise mechanism, the left ventricle is divided into a large, high-pressure region below the area of apposition and a smaller, low-pressure region beyond the point of contact. The cardinal features of dynamic LVOT obstruction are the variability and lability of the resulting systolic pressure gradient. Any intervention or physiologic change that decreases systemic vascular resistance, reduces preload, or increases left ventricular contractility results in enhancement of the obstruction. Exercise, for example, dramatically increases the gradient across the LVOT, and isoproterenol is sometimes administered for diagnostic purposes to mimic exercise and provoke a latent gradient.[195]

Mitral regurgitation is observed in most patients with the obstructive form of HCM, presumably because of the structural and functional abnormalities already described. Other consequences of LVOT obstruction include increased wall stress, increased myocardial oxygen consumption, reduced coronary blood flow, and myocardial ischemia. Tachycardia worsens dynamic LVOT obstruction and all its adverse consequences. The precise relationship between myocardial hypertrophy and dynamic obstruction is uncertain. There is little correlation between the degree of hypertrophy and the presence or severity of LVOT obstruction in human patients. In litters of affected puppies examined by one of us (Sisson), the degree of myocardial hypertrophy was directly proportional to the severity of the outflow tract obstruction. Furthermore, LV hypertrophy tends to regress in some dogs when their dynamic obstruction is eliminated by beta-blockers. These observations suggest that myocardial hypertrophy is, at least in some dogs and to some degree, a consequence of the dynamic LVOT obstruction.

HISTORY AND PHYSICAL EXAMINATION

Most dogs with HCM manifest no clinical signs and have no history of physical impairment. Most affected dogs have been identified when a heart murmur or arrhythmia prompted further diagnostic evaluation. Other cases are detected only at necropsy or following sudden death. Sudden death seems to occur most often during or immediately after exertion. Syncope and near-syncope have been noted in a few affected dogs. Occasionally, dogs are presented for reduced exercise capacity, or respiratory distress. Too few dogs have been studied to correlate the risk of death or the severity of clinical signs with the presence or severity of outflow obstruction. No such correlation has been found in affected human patients.[6] There is a general relation between the severity of symptoms and the severity of left ventricular hypertrophy in human patients. However, many people demonstrate incapacitating symptoms in the face of mild LV hypertrophy, and many people with severe hypertrophy have mild or no symptoms.[6]

A systolic heart murmur is the most common abnormality detected on physical examination, but it is consistently found only in those dogs with dynamic LVOT obstruction. The systolic ejection murmur resulting from dynamic obstruction is best heard (loudest) at the left-sided heart base. An equally loud murmur is sometimes heard at the left apex associated with mitral valve insufficiency caused by SAM of the mitral valve. The heart murmur may be soft or absent at rest, but it is usually readily heard when exercise (short jog) or excitement (toe pinch) increases heart rate by 30 to 40 bpm. The murmur can also be evoked by administration of a drug that increases heart rate, reduces afterload, or increases contractility (e.g., acepromazine). The intensity and character of the murmur are often inconsistent from one examination to the next. Importantly, some dogs with HCM have no abnormalities on physical examination.

RADIOGRAPHIC AND ECG CHANGES

Radiographic changes are often modest in dogs with HCM since LV concentric hypertrophy causes little change in the external size of the heart unless it is severe (Fig. 27–10). Modest to moderate left atrial enlargement may be observed with or without evidence of left ventricular enlargement. Enlargement of the pulmonary veins and pulmonary edema are observed in dogs with elevated LV diastolic and left atrial pressures. In dogs with moderate to severe LV

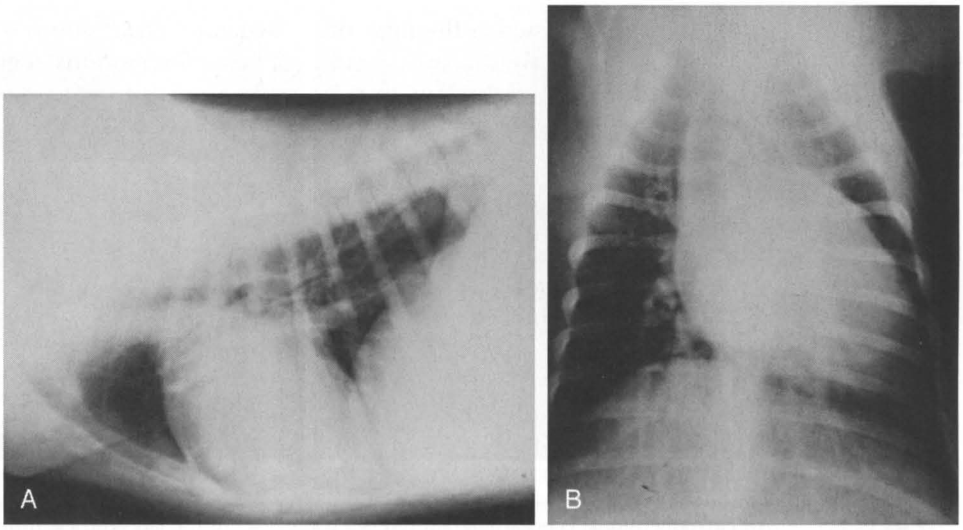


FIGURE 27–10

Lateral (A) and dorsoventral (B) radiographs of a dog with hypertrophic cardiomyopathy, showing moderate left heart enlargement. (From Thomas WP, et al. Hypertrophic obstructive cardiomyopathy in a dog: clinical, angiographic, and pathologic studies. J Am Anim Heart Assoc 20:253, 1984.)

hypertrophy, some evidence of left ventricular enlargement is usually evident on the resting electrocardiogram. High-amplitude R waves are particularly prominent on the left precordial chest leads (V_2 and V_4), and they are also commonly observed on leads II, III, and aV_F. Left axis deviation is uncommon. Arrhythmias reported in a small number of dogs with HCM include ventricular premature beats, paroxysmal ventricular tachycardia, and first-degree and third-degree AV block.[191–194]

ECHOCARDIOGRAPHY

Two-dimensional echocardiography is the best method for confirming a diagnosis of HCM. The most common echocardiographic feature of canine HCM is the presence of left ventricular concentric hypertrophy (Fig. 27–11). Left ventricular hypertrophy is global, and it tends to be symmetric rather than asymmetric.[7] A muscular ridge of myocardium is sometimes present in the LVOT, and this is most easily appreciated on a short-axis view where it assumes the appearance of an accessory papillary muscle. Other features include left atrial enlargement, reduced size of the left ventricular lumen, SAM of the mitral valve with narrowing of the LVOT (Fig. 27–11), increased velocity of blood flow across the LVOT, and mitral valve insufficiency. The severity of LVOT obstruction detected by spectral Doppler varies depending on heart rate and the level of patient anxiety. Evidence of obstruction may be entirely absent in the resting patient but is often readily provoked by a toe pinch. It is often difficult to assess the severity of a dynamic obstruction on a resting Doppler examination. Provocative intervention, such as isoproterenol infusion, often unmasks a latent obstruction and gives some indication of the patient's response to exercise. No systematic echocardiographic studies of diastolic function have been reported in dogs with HCM. In some dogs, the amplitude of the mitral valve A wave is increased and the E/A ratio is reduced, suggesting reduced compliance. Prolongation in the isovolumetric relaxation time and an increase in the deceleration time of the spectral Doppler mitral valve E wave may also be observed.

TREATMENT AND PROGNOSIS

The severity and consequences of HCM in dogs and people are quite variable. Survival to at least middle age without clinical signs has been documented in some affected dogs, but others have died suddenly or developed signs of congestive heart failure.[191–200] One of us (Sisson) has observed spontaneous disappearance of LVOT obstruction and resolution of hypertrophy in some immature dogs after they reached adulthood (1 to 2 years of age). Other dogs have achieved this status after prolonged medical therapy to reduce dynamic obstruction; some dogs require lifelong treatment. Too few dogs have been treated to draw definitive conclusions regarding the best treatment for canine HCM. The goals of treatment in cats and humans with HCM are to improve diastolic filling, alleviate congestive signs, reduce or abolish obstructive gradients, control arrhythmias, and prevent sudden death (see chapter 18). Since most of the dogs we have evaluated have severe dynamic outflow obstruction with no evidence of CHF, treatment eliminating or reducing the obstruction and preventing sudden death has been largely emphasized.

Options for treating dynamic LVOT obstruction include drug therapy, surgery, pacemaker implantation, and selective alcoholization of the interventricular septum. Beta-adrenoreceptor–blocking drugs are often used to reduce dynamic LVOT obstruction in human patients. By slowing the heart rate, beta-blockers also improve diastolic filling, but they do not improve myo-

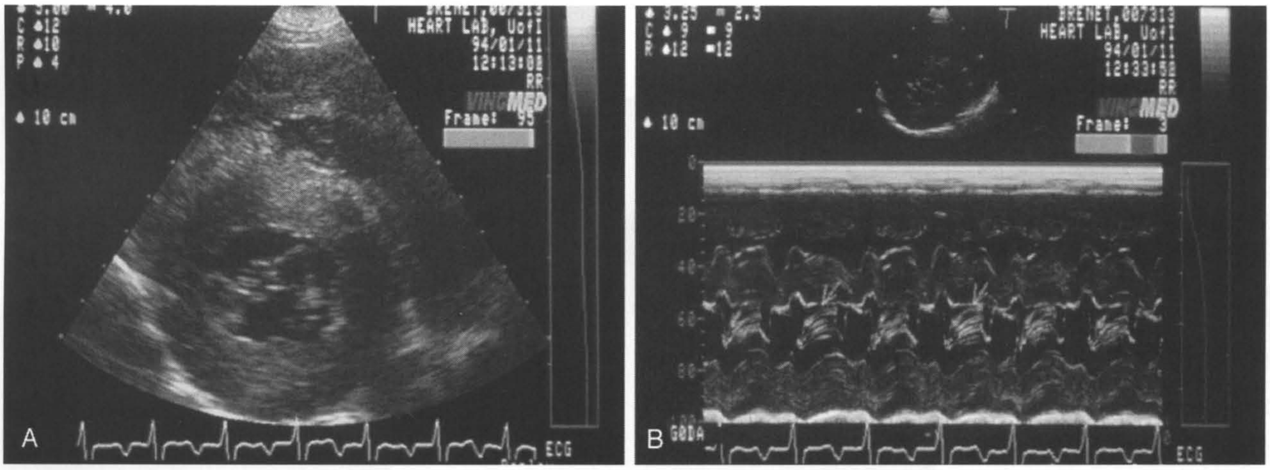


FIGURE 27–11

(A) Two-dimensional echocardiogram (cross-section view) of the left ventricle through the mitral valve. The left ventricle is concentrically hypertrophied, and systolic apposition of the mitral valve with the interventricular septum is present during midsystole (SAM). (B) Systolic anterior motion of the mitral valve, with systolic apposition with the septum *(arrows)* is evident on this M-mode echocardiogram.

cardial relaxation.[213, 215, 216] We have been able to abolish or reduce markedly the severity of LVOT obstruction in most of the dogs we have treated with beta-blockers. Atenolol is usually very effective, but other beta-blockers probably work as well. The dose of atenolol is gradually increased, from 0.5 to 1.5 mg/kg q12 to 24h until the gradient is abolished or adverse signs (lethargy, bradycardia) are observed. The calcium channel blocker verapamil has also been shown effective in reducing dynamic obstruction in human patients by virtue of its negative inotropic effects.[212, 213, 215] We have not used this drug in dogs with HCM. Verapamil improves diastolic filling by improving ventricular relaxation and reducing heart rate.[212] Diltiazem is less effective for reducing LVOT obstruction as it does not depress contractility as markedly as do verapamil or beta-blockers.[212, 217] Because of its vasodilating effects, diltiazem can worsen dynamic obstruction in some patients. Diltiazem might be more useful for treating the nonobstructive form of canine HCM, given its beneficial effects on ventricular relaxation and diastolic filling. Diuretics have been shown to improve congestive symptoms in humans with HCM, and conservative dosing does not appear to aggravate LVOT obstruction substantially. Few affected dogs have required such treatment.

A number of ingenious alternatives have been devised to diminish the LVOT obstruction when drug therapy is contraindicated or ineffective. In some patients, the dynamic LVOT obstruction can be reduced or abolished by altering the normal sequence of ventricular activation. Paradoxic motion of the interventricular septum can be induced by dual-chamber (DDD) pacing, thereby reducing SAM and the obstructive gradient.[215] In some human patients treated by DDD pacing, a prolonged beneficial effect persists even when pacing is discontinued.[218, 219] To our knowledge, only one dog has been treated in this fashion. Surgical myectomy of the hypertrophied septum with or without simultaneous repair or replacement of the mitral valve can also be used to abolish obstruction by preventing SAM of the mitral valve.[1, 220, 221] This technique is often helpful in human patients but has not been attempted in dogs. Septal hypertrophy can also be obliterated without surgery by alcoholization of the interventricular septum (Sigwart procedure).[222]

Strenuous exercise should be discouraged because of the risk of sudden death. Aggressive treatment with beta-blockers helps encourage this recommendation. The value of antiarrhythmic drug therapy in humans with HCM is controversial.[1, 6] Amiodarone and sotalol, both of which are class III antiarrhythmic drugs, are useful for treating symptomatic arrhythmia in patients with HCM, but there is no conclusive evidence that they improve survival (see chapter 18).[1] Implantable cardiac defibrillators are sometimes used in human patients considered at high risk for sudden death.[223] These modalities have not been evaluated in dogs with HCM.

UNUSUAL OR UNCLASSIFIED MYOCARDIAL DISEASES

CANINE X-LINKED MUSCULAR DYSTROPHY

Dystrophin is a protein that binds actin and, together with a complex of other proteins, links the cytoskeleton to the extracellular matrix.[224] Mutations in the dystrophin gene result in progressive degenera-

tion of systemic and cardiac muscle.[225] Duchenne's and Becker's muscular dystrophy, collectively referred to as the dystrophinopathies, are the most common inherited muscular diseases in people. Cardiac involvement is characterized pathologically by degeneration and fibrosis of the myocardium, centering on the posterolateral wall of the left ventricle. Myocardial failure is the eventual culmination of these changes. Canine X-linked muscular dystrophy (CXMD) is a rare muscular disease that shares many similarities with Duchenne's and Becker's muscular dystrophies in people. It is sometimes referred to as golden retriever muscular dystrophy (GRMD) because it was first recognized in golden retriever dogs, some of which were bred and developed as a model of this disorder.[226–228] GRMD is caused by a point mutation in the consensus splice acceptor in intron 6 of the canine dystrophin gene. As a result, exon 7 is skipped during processing of the GRMD dystrophin messenger RNA.[229]

Myocardial lesions are not grossly visible prior to 11 weeks of age, but they become obvious by 6.5 months of age and are quite extensive by 6 years of age. Early lesions, consisting of focal areas of myocyte degeneration and mineralization, first appear in the subepicardial region of the LV free wall, the LV papillary muscles, and interventricular septum. These later evolve into linear and anastomosing bands of loose fibrovascular tissue and eventually into dense fibrous connective tissue. The most common ultrastructural features of CXMD are increased variation in myocyte size and endomysial fibrosis. Other changes include loss of myofilaments, increased numbers of variable-sized mitochondria, and increased myelin, cytoplasmic lipofuscin, and lipid droplets. Immunohistochemical staining can be employed to identify affected dogs.[225–227]

Clinical signs of skeletal muscle involvement predominate in affected dogs, but severe cardiac involvement often develops later in life. Signs of skeletal muscular dystrophy appear at about 8 weeks of age and dominate the clinical picture during the first few years of life. Only a few dogs, most raised in breeding colonies, have survived until 5 or 6 years of age, when signs of CHF become obvious.[227] Some dogs develop soft systolic murmurs typical of mild mitral insufficiency. The ECG changes in CXMD are most obvious when sequential tracings are obtained after 6 months of age. Abnormalities include a shortened PR interval, deep and narrow Q waves in leads II, III, aV_F, CV6LL, and CV6LU, and an increased Q/R ratio in leads CV6LL and CV6LU.[228] Ventricular premature complexes and ventricular tachycardia have also been observed. Radiographic cardiomegaly is usually modest, but the cardiac apex may be distinctly pointed.[228] Distinctive echocardiographic changes are observed in dogs over 6 months of age. Hyperechoic myocardial lesions first appear and become most extensive in the left ventricular free wall and papillary muscles, and to a lesser extent in the septum (Fig. 27–12). The intensity of the hyperechoic areas decreases after 2 years of age when the dimensions of the left ventricle increase as LV contractility begins to decline, as demonstrated by decreased fractional shortening, increased E point septal separation, and hypokinesis of the septum and LV wall. Signs of CHF can be treated by traditional means, but specific treatment for CXMD is not currently available.

ATRIOVENTRICULAR MYOPATHY (SILENT ATRIA, PERSISTENT ATRIAL STANDSTILL)

Atrioventricular myopathy (AVM) is a progressive myocardial disease of dogs and cats that is character-

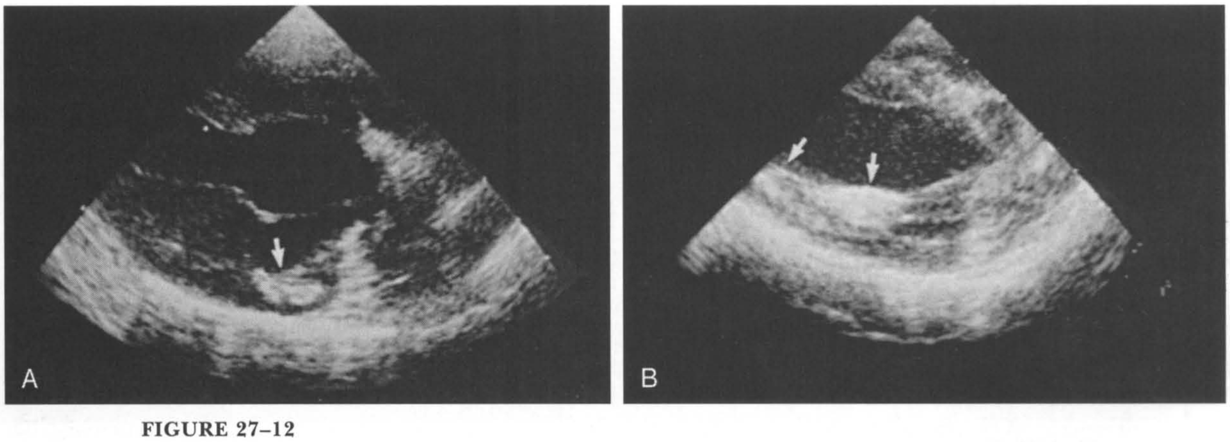


FIGURE 27–12

Two-dimensional echocardiograms recorded from a 7-month-old female dog (A) and an 8-month-old male dog (B) with Duchenne-type muscular dystrophy. Modified parasternal long-axis views of the LV show hyperechoic lesions clumped in the left ventricular free wall at the level of the chordae tendineae *(arrow)* in (A), and in the papillary muscle and LV free wall *(arrows)* in (B). (From Moise NS, et al. Duchenne's cardiomyopathy in a canine model: electrocardiographic and echocardiographic studies. J Am Coll Cardiol 17:812, 1991. Copyright by the American College of Cardiology.)

ized by atrial enlargement, bradycardia, eventual heart failure, and death. Some affected dogs have a poorly characterized form of skeletal muscular dystrophy.[230] English springer spaniels and Old English sheepdogs are reportedly predisposed, but AVM also occurs in other pure- and mixed-breed dogs. Affected dogs typically present for weakness, collapse, or syncope caused by severe bradycardia. Less commonly, dogs present with signs of right or biventricular CHF. Soft murmurs of AV valve insufficiency are audible in many cases. The most common ECG abnormality is persistent atrial standstill, but heart block and other rhythm and conduction disturbances also occur. Atrial enlargement is usually evident on thoracic radiographs, and generalized cardiomegaly is present in some dogs. Dilated, immobile atria can be identified by echocardiography or fluoroscopy. In some cases, the atrial appendage(s) continue to contract after activity in the rest of the atria has ceased. The clinical course of AVM is characterized by declining myocardial contractility, progressive ventricular dilation, and the development of refractory heart failure. Signs resulting from bradycardia can be palliated by artificial pacemaker implantation, but most dogs soon develop clinical signs of progressive heart failure.

At necropsy, the atria are often dilated, thin, and fibrotic, with little or no visible muscle (Fig. 27–13).[230] The atrial appendages are often less severely affected than the rest of the atria. Histologic findings include variable amounts of mononuclear infiltration, myofiber necrosis and disappearance, and pervasive replacement fibrosis. In some cases, the inflammatory infiltrates are extensive (Fig. 27–13).[231] Changes in skeletal muscle include muscle atrophy, hyalinized degenerated muscle fibers, and mild to moderate steatosis. Cardiomyopathy and conduction disturbances also characterize Emery-Dreifuss and some limb girdle muscular dystrophies in people.[232–235] The relationship between canine AVM and these disorders is uncertain. Emery-Dreifuss muscular dystrophy (EDMD) is an X-linked inherited muscular disorder characterized by the triad of progressive weakness in humeroperoneal muscles and cardiomyopathy with conduction block. The gene responsible for X-linked EDMD encodes a serine-rich protein of 254 amino acids, named emerin, located in the nuclear envelope and in desmosomes and fasciae adherentes of cardiac myocytes.[233] Eight other dystrophin-associated muscle proteins, including dystroglycans, 5 sarcoglycans, and utrophin, have been identified.[234] Absence of alpha-sarcoglycan in some people is associated with the presence of dilated cardiomyopathy and the propensity to develop atrioventricular (AV) conduction disturbances.[235]

RIGHT VENTRICULAR CARDIOMYOPATHY

Right ventricular cardiomyopathy, sometimes referred to as arrhythmogenic right ventricular dysplasia, is an unusual heart disorder in people characterized by partial or total replacement of the right ventricular muscle with adipose and fibrous tissue.[1, 236] In people, diagnosis is based on the echocardiographic demonstration of a dilated, poorly contracting right ventricle,

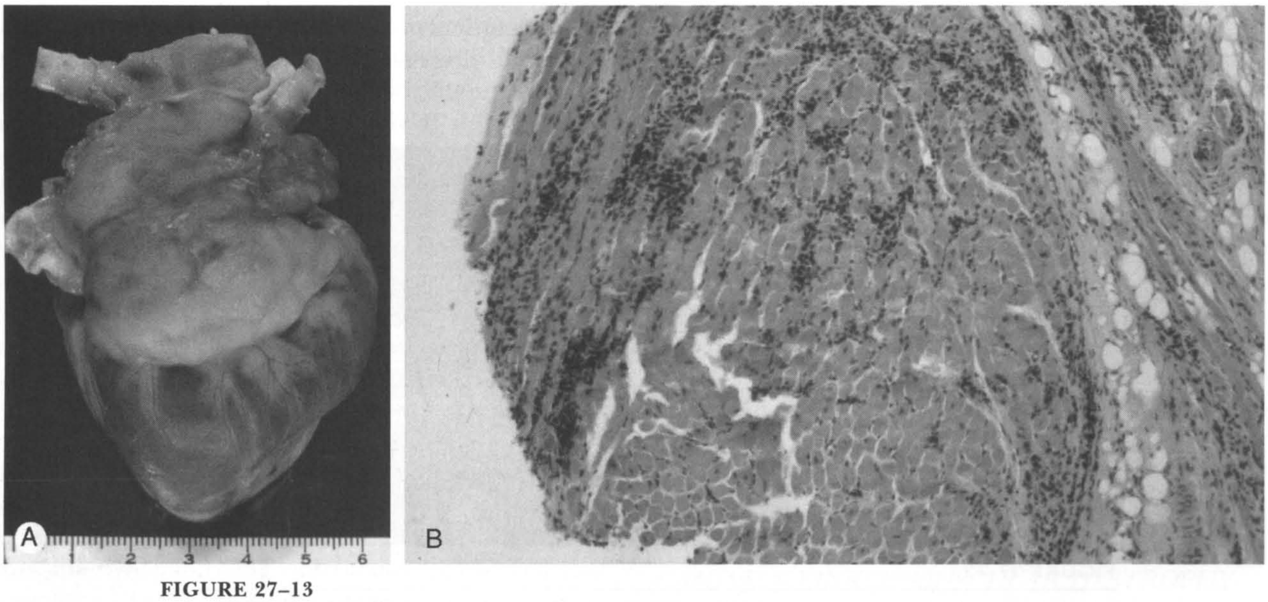


FIGURE 27–13

(A) This right-sided external view of the heart of a dog with atrioventricular myopathy shows a very dilated right atrium, and the atrial myocardium has been largely replaced by fibrous connective tissue except for the tip of the right auricle. (Photo courtesy of Dr. W. P. Thomas.) (B) The histology specimen from a different dog with AVM shows extensive mononuclear cell infiltrates surrounding healthy and dying atrial myocytes.

the finding of inverted T waves in the right precordial ECG leads, ventricular arrhythmias of right ventricular origin, and symptoms of palpitations and syncope. Autosomal dominant inheritance has been shown in about one third of human cases. Similar pathologic and clinical findings were described in the only two canine cases reported to date.[237, 238] Fox has recently described this condition in cats (see chapter 28).

SECONDARY MYOCARDIAL DISEASES OF DOGS

NONINFECTIOUS MYOCARDIAL DISEASES

DRUGS AND TOXINS

Many drugs and toxins have been shown to cause temporary myocardial depression (anesthetics) or permanent myocardial injury. High cumulative doses of alcohol, cobalt, gossypol, catecholamines, furazolidone, monensin, and a number of anticancer chemotherapeutic agents cause degenerative myocardial lesions and cardiac failure.[7, 239] With the exception of chemotherapeutic agents, natural exposure to large quantities of these toxins is unlikely. Most cases of drug-induced myocardial failure in dogs are caused by the administration of the anthracycline compound doxorubicin to cancer patients.[240–244] The 4′-anthracycline analogue epirubicin is also cardiotoxic, although it is reportedly less so than doxorubicin.[245] Mitoxantrone, a dihydroxyquinone derivative of anthracene related to doxorubicin, is reported to have no or very little cardiotoxicity in dogs, but this is yet to be confirmed.[246] High doses of cyclophosphamide are also cardiotoxic, particularly when given in combination with doxorubicin.[1, 247]

ANTHRACYCLINE CARDIOTOXICITY. Doxorubicin is used to treat many different types of cancer. Standard use of rather high doses has resulted in a large increase in the frequency of acute and chronic cardiotoxicity. The toxic mechanism of myocardial cell injury is uncertain, but free radical generation and lipid membrane peroxidation may be involved. Pathologic changes caused by doxorubicin include myocyte degeneration with myofibrillar loss, cytoplasmic vacuolization, myocytolysis, and interstitial fibrosis and edema.[1, 241] Less severe myocyte injury has been demonstrated after a single injection of doxorubicin.[248] Even when the cumulative dose is low, doxorubicin infusion can cause supraventricular or ventricular arrhythmias. These rhythm disturbances are rarely severe and generally do not require treatment. Chronic doxorubicin toxicity causes progressive myocardial failure. Myocardial failure with signs of CHF can occur in dogs receiving cumulative doses of 150 to 240 mg/m^2.[240–244] Persistent arrhythmias and conduction disturbances are also associated with high (over 150 mg/m^2) cumulative dosages, and their occurrence does not necessarily correlate with advanced myocardial failure.[240–242] Once thought to be a rapidly progressive and uniformly fatal complication, doxorubicin-induced myocardial failure can be successfully treated, with a reasonably favorable outcome, at least in human patients.[249, 250] Several studies indicate that many patients improve with conventional heart failure treatment, and they have reasonably long survival times.[249, 250]

The overall prevalence of doxorubicin toxicity is unknown. In one study of 175 dogs, 18 percent developed cardiac abnormalities, but only 4 percent developed signs of CHF.[243] The reported prevalence of CHF in dogs treated for lymphosarcoma has varied from 8 percent to 16 percent.[243, 251] Of 35 dogs with osteosarcoma treated with doxorubicin at a cumulative dose of 150 mg/m^2, three died or were euthanized because of cardiomyopathy and one dog died suddenly.[252] The most important risk factor for cardiotoxicity identified in dogs is the total cumulative dose of doxorubicin. Risk factors identified in people include (1) high cumulative total dose; (2) high peak serum levels (high single doses given over a short time period); (3) concurrent administration of other cardiotoxic drugs; such as cyclophosphamide; (4) patient age, with very young and very old patients at greatest risk; and (5) history of cardiac disease.

The time to onset of CHF, relative to the last administered doxorubicin treatment, is highly variable. Echocardiographic evidence of moderate to advanced myocardial failure may be seen during or shortly after treatment or may develop several months following cessation of treatment. It is advisable to monitor doxorubicin therapy periodically via resting ECGs and echocardiography. There are no agreed upon criteria for the administration and monitoring of doxorubicin in dogs, but the following approach serves as a pragmatic guide: Chest radiographs and an ECG should be obtained before initiating therapy. Dogs with suspected heart disease and those breeds at high risk for DCM, such as Doberman pinschers, should be evaluated by echocardiography prior to initiating doxorubicin. In most circumstances, doxorubicin should be avoided in dogs with a fractional shortening (FS) of less than 20 percent. After receiving a 90 mg/m^2 cumulative dosage of doxorubicin, every dog should be evaluated by echocardiography, which should be repeated after each subsequent dose. An earlier evaluation should be scheduled if arrhythmias or exercise intolerance is detected. Treatment with doxorubicin should be discontinued if the percent FS declines below 25 percent, unless there is no other reasonable treatment alternative. Efforts continue to identify an effective cardioprotectant for patients receiving high cumulative

doses of doxorubicin. At least one such agent, dexrazoxane, has shown efficacy in humans and dogs, but the optimal dose in dogs has not been determined.[253]

INFILTRATIVE AND RESTRICTIVE CARDIOMYOPATHIES

Infiltrative myocardial diseases are rare in dogs. The most common infiltrating cardiac tumors occurring in dogs are hemangiosarcoma, some heart base tumors, and lymphosarcoma. Diastolic or systolic myocardial dysfunction caused by diffuse myocardial infiltration is very rare. Lymphosarcoma is the most likely tumor to exhibit this behavior.[7] Myocardial lymphosarcoma is sometimes so extensive that it resembles hypertrophic cardiomyopathy on echocardiography. The clinical manifestations of cardiac neoplasia are usually due to pericardial effusion, local obstruction to blood flow, or arrhythmia. The diagnosis and treatment of the common cardiac neoplasms are discussed in chapters 29 and 36.

Other diseases reported to cause restrictive myocardial disease in humans, such as amyloidosis, sarcoidosis, hemochromatosis, and eosinophilic or fibrosing endomyocardial disease, have not been reported in dogs. Myocardial infiltration with glycogen has been reported in several Lapland dogs with type II glycogen storage disease (Pompe's disease).[254, 255] Clinical signs were mainly due to profound skeletal muscular weakness and megaesophagus. None of the dogs had signs of CHF, but cardiac arrhythmias and cardiomegaly were identified. Identification of the enzymatic defect was accomplished by demonstration of decreased acid alpha-glucosidase activity in peripheral blood leukocytes. Autosomal recessive inheritance was suspected.

ISCHEMIC CARDIOMYOPATHY

Ischemic myocardial disease can result from obstruction of the large coronary arteries, from obstruction of the smaller intramural coronary arterioles, or from intense and prolonged vasospasm. Of the few cases of myocardial infarction reported in the literature, most had bacterial endocarditis with coronary artery embolization.[256, 257] Myocardial infarcts have also been reported secondary to septicemia and pulmonary neoplasms, and as the primary disorder in cases of sudden, unexpected death.[7, 258] Liu and associates described the clinical and pathologic findings in 21 dogs with atherosclerosis.[259] In this study, four dogs showed signs of heart failure, and three dogs had atrial fibrillation. Hypothyroidism, hypercholesterolemia, and hyperlipidemia were identified as possible risk factors. The low incidence of atherosclerosis in dogs is most likely related to genetic, diet, and lifestyle differences relative to humans. In addition, the dog has an extensive epicardial collateral vascular network that is absent in humans. Diagnosis of myocardial infarction is difficult, and it is probably seldom recognized antemortem. Arrhythmias, altered QRS complexes with deep Q waves, ST segment changes, and T-wave abnormalities may be detected.[256] Asymmetric hypokinesis may be observed by echocardiography. Increased aspartate transaminase (AST, SGOT) and creatine kinase (CK) activity has been observed by us in association with weakness, depression, ventricular tachycardia, and subsequent death associated with extensive myocardial infarction.

Myocardial necrosis and fibrosis are often observed in the papillary muscles and subendocardial regions of the left ventricle in dogs dying of subvalvular aortic stenosis or hypertrophic cardiomyopathy. Such lesions are usually seen in association with intimal proliferation and hypertrophy of the smooth muscle in the media of the intramural coronary arteries. The subendothelial myocardium is most distant from the origin of the intramural circulation and is most subject to compromise of the coronary circulation, whether it results from physical obstruction, high intramural pressure, or tachycardia. Similar myocardial lesions are commonly observed in old dogs with chronic degenerative valve disease in association with arteriosclerotic lesions of the small intramural arterioles (see chapter 25). Myocardial necrosis may also result from coronary vasoconstriction caused by increased catecholamine levels. Myocardial ischemic necrosis due to sympathetically mediated coronary vasoconstriction may occur secondary to shock, severe hypotension, and central nervous system lesions, especially brain and spinal cord trauma.[260, 261]

MYOCARDITIS

Myocarditis, simply defined, is a focal or diffuse involvement of the heart muscle in an inflammatory process. It can result from a variety of infectious, chemical, or physical agents.[1] Although the term is often used in association with arrhythmic diseases in dogs, myocarditis is usually not proved in these cases. The consequences of myocarditis depend on the location, extent, and duration of cardiac involvement. Endomyocardial biopsy is essential for antemortem diagnosis, and this may explain, in part, why life-threatening acute myocarditis and subacute myocarditis with subsequent myocardial failure are not diagnosed very often in dogs. Focal myocarditis may go unnoticed and undiagnosed unless an important area such as the conduction system is involved. Subclinical or mild myocarditis is probably common in a variety of infectious and noninfectious systemic illnesses, but the diagnosis is rarely proved.

VIRAL MYOCARDITIS

Although many viruses probably have the potential for causing myocarditis, few have been proved clini-

cally or experimentally in the dog, and these appear to be age-dependent, with a short window of susceptibility in the first few weeks of life. In the late 1970s and the early 1980s, a worldwide epidemic of canine parvovirus infection in dogs occurred. During that epidemic, a peracute viral myocarditis with very high mortality was described in litters of puppies between 3 and 10 weeks of age.[262–267] Clinical signs included sudden, unexpected death or peracute onset of anorexia and tachypnea progressing to death from pulmonary edema within minutes to hours. Clinical evaluation of affected pups showed tachycardia, arrhythmias, gallop rhythms and apical systolic murmurs, pulmonary rales, cardiomegaly, and pulmonary infiltrates, indicative of acute, severe left-sided heart failure. At necropsy, the hearts were dilated and the myocardium was pale. The histologic hallmark was myocarditis characterized by mononuclear cell infiltration and dense basophilic intranuclear inclusion.[263–266] Since 1982, this form of canine parvoviral disease has become rare, probably due to widespread immunity from natural exposure or vaccination. Convincing clinical and experimental evidence indicates that myocardial failure in young dogs less than a year old may be the result of a prior parvovirus infection. Clinically, such cases may be indistinguishable from other forms of DCM.[267–271]

Whether or not natural viral infections of other types produce myocarditis is uncertain. Certainly, no common syndromes are recognized. Experimental infections of puppies with both canine distemper virus and herpesvirus can produce myocarditis.[272, 273]

PROTOZOAL MYOCARDITIS

TRYPANOSOMIASIS (CHAGAS' DISEASE). Chagas' disease has been reported in young dogs from the southern United States and Central and South America.[274–278] The infecting organism, *Trypanosoma cruzi*, is a protozoan parasite transmitted by a blood-sucking insect of the subfamily Triatoma. Enzootic infections have been identified in some populations of wild animals, rodents, and dogs.[274–279] The acute stage of the disease is characterized by weight loss, diarrhea, lethargy, anorexia, lymphadenopathy, myocarditis, and sudden death. Acute infection is followed by a long latent phase of infection and the late but frequent development of progressive myocardial disease. Immunologic phenomena are thought to play an important role in the pathogenesis of chronic myocardial disease, which is characterized by the development of a variety of arrhythmias and conduction disturbances, and eventually, by chamber enlargement and signs of heart failure. Investigators in Panama recently described the clinical course of Chagas' disease in 44 naturally infected dogs, which apparently serve as chronic reservoirs of infection.[278] The most common ECG abnormalities were ventricular and atrial arrhythmias and second-degree AV block. Dilation of the right atrium and right ventricle eventually culminated in heart failure.

Antemortem diagnosis requires demonstration of parasitemia by culture or xenodiagnosis, or serodiagnosis using complement fixation or other tests. Pathologic examination shows multiple pale areas in the myocardium, especially in the right atrium and ventricle. Active granulomatous myocarditis is characterized by infiltrates of lymphocytes, plasma cells, and macrophages associated with clusters of *T. cruzi* amastigotes (Fig. 27–14; see also Figs. 36–9, 36–10). In chronically infected dogs, fibrosis is often extensive in the right atrium and right ventricle and around the conduction system.[280–282]

TOXOPLASMOSIS AND NEOSPOROSIS. The long-lived bradyzoites of *Toxoplasma gondii* can encyst in the myocardium, producing a chronic infection. Subsequent recrudescence and cyst rupture result in myocardial necrosis and hypersensitivity reactions, resulting in myocarditis, pericarditis, and, on rare occasion, heart failure. Serologic testing with demonstration of rising titers is helpful in establishing the diagnosis.[283] *Neospora caninum* infects multiple tissues, including the heart, peripheral muscles, and central nervous system. Peripheral neuromuscular deficits and CNS signs often dominate the clinical presentation, but collapse and sudden death have been reported in some affected

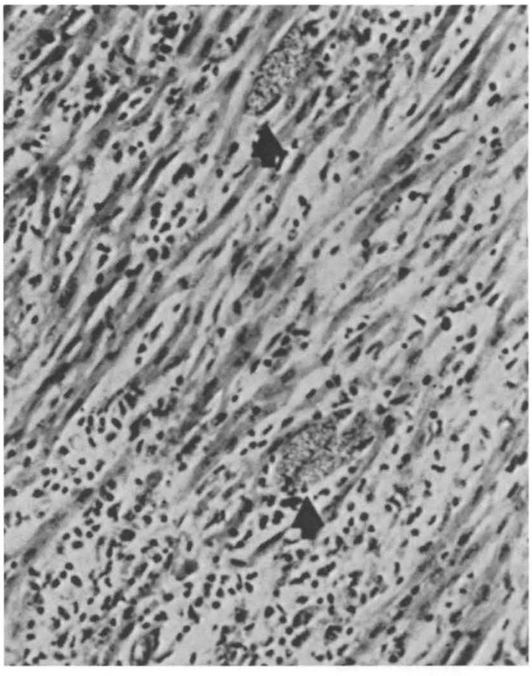


FIGURE 27–14

Histopathology of trypanosomal (Chagas') myocarditis from a dog. A mixed neutrophilic and mononuclear cell infiltrate is visible in association with clusters of *T. cruzi* amastigotes *(arrows)*. H&E stain × 100. (From Williams GD, et al. Naturally occurring trypanosomiasis (Chagas' disease) in dogs. J Am Vet Med Assoc 171:171, 1977.)

dogs.[284, 285] The diagnosis can be confirmed by immunohistochemistry, electron microscopy, and the demonstration of antibodies to *Neospora caninum.* Severely ill dogs often die, but successful treatment has been reported with clindamycin, potentiated sulfonamides, and/or pyrimethamine.[283, 286]

BACTERIAL AND MYCOTIC MYOCARDITIS

Bacterial myocarditis is a possibility whenever bacteremia, sepsis, or endocarditis occurs (see Fig. 36–8). The most common offending agents are staphylococcal and streptococcal species.[287–289] Suppurative myocarditis often develops in patients with bacterial endocarditis, either via direct extension from an infected valve or via the coronary circulation (see chapter 26). Myocardial damage is sometimes caused by bacterial toxins or by immune-mediated processes. Cardiac arrhythmias are the principal clinical manifestation of bacterial myocarditis. Lyme disease is a commonly mentioned cause of myocarditis in dogs, but documented cases with proven cardiac sequelae are exceedingly rare. Lyme disease (borreliosis) is a multisystemic disease dominated by involvement of joints, the CNS, eyes, and skin.[290–292] Clinical signs reported in dogs are often vague and nonspecific. Lyme disease is caused by the spirochete *Borrelia burgdorferi* and is transmitted principally by the deer tick, *Ixodes dammini.* Most cases of Lyme disease occur in the northeastern, western coastal, and north central United States. Serologic testing is not at present a reliable method of diagnosis.[290–292] The organism is difficult to isolate from tissues, but its presence may be surmised by positive immunohistochemical staining. Histologic changes associated with Lyme myocarditis include multifocal myocardial necrosis and a mixed cellular infiltrate of plasma cells, lymphocytes, neutrophils, and macrophages.

Fungal infections of the myocardium are extremely rare, and they tend to occur mainly in debilitated or immunosuppressed patients. Infection usually spreads to the heart hematogenously, but local invasion can also occur. Mycotic cardiac infections reported in dogs include cryptococcosis, coccidioidomycosis, aspergillosis, and those due to other saprophytic fungi.[293–300]

REFERENCES

1. Wynne J, Braunwald E. The cardiomyopathies and myocarditides. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 5th ed. Philadelphia, WB Saunders, 1997, p 1404
2. Fox PR. Myocardial diseases. *In* Ettinger SJ (ed): Textbook of Veterinary Internal Medicine. 3rd ed. Philadelphia, WB Saunders, 1989, p 1097
3. Fox PR. Canine myocardial disease. *In* Fox PR: Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 467
4. Thomas WP. Myocardial diseases of the dog. *In* Bonagura JD (ed): Contemporary Issues in Small Animal Practice. Cardiology. New York, Churchill Livingstone, 1987, p 117
5. Edwards WD. Cardiomyopathies. Hum Pathol 18:625, 1987
6. Wynne J, Braunwald E. The cardiomyopathies and myocarditides: toxic, chemical, and physical damage to the heart. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB Saunders, 1992, p 1394
7. Sisson DD, Thomas WP. Myocardial diseases. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 995
8. Report of a World Health Organization (WHO) Expert Committee on Cardiomyopathies, WHO Technical Report Series 697, Geneva, 1984, p 7
9. Buchanan JW. Causes and prevalence of cardiovascular disease. *In* Kirk RW, Bonagura JD (eds): Kirk's Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 647
10. Detweiler DK, Patterson DF. Prevalence and types of cardiovascular disease in dogs. Ann NY Acad Sci 127:481, 1965
11. Fioretti M, Delli Carri E. Epidemiological survey of dilatative cardiomyopathy in dogs. Abstract. Veterinaria 2:81, 1988
12. Codd MB, Sugrue DD, Gersh BJ, et al. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy: a population-based study in Olmsted County, Minnesota. Circulation 80:564, 1989
13. Manolio TA, Baughman KL, Rodeheffer R, et al. Prevalence and etiology of idiopathic dilated cardiomyopathy (summary of a National Heart, Lung, and Blood Institute workshop). Am J Cardiol 69:1458, 1992
14. Ettinger S, Lusk R, Brayley K, et al for the Cooperative Veterinary Enalapril (COVE) Study Group. Evaluation of enalapril therapy in dogs with heart failure in a large multicenter study. Proceedings, 10th Annual Veterinary Medical Forum, ACVIM, 1992, p 584
15. Tidholm A, Svensson H, Sylvén C. Survival and prognostic factors in 189 dogs with dilated cardiomyopathy. J Am Anim Hosp Assoc 33:364, 1997
16. Sleeper M, Lankford E, Dambach D, et al. Portuguese water dog cardiomyopathy. Abstract. J Vet Intern Med 12:248, 1998
17. Darke PGG, Else RW. Canine cardiomyopathy. Vet Annu 24:237, 1984
18. Monnet E, Orton EC, Salman M, et al. Idiopathic dilated cardiomyopathy in dogs: survival and prognostic indicators. J Vet Intern Med 9:12, 1995
19. Calvert CA, Chapman WL Jr, Toal RL. Congestive cardiomyopathy in Doberman pinscher dogs. J Am Vet Med Assoc 181:598, 1982
20. Calvert CA. Dilated congestive cardiomyopathy in Doberman pinschers. Compend Cont Educ 8:417, 1986
21. Calvert CA, Brown J. Use of M-mode echocardiography in the diagnosis of congestive cardiomyopathy in Doberman pinschers. J Am Vet Med Assoc 189:293, 1986
22. Calvert CA, Pickus CW, Jacobs GJ, et al. Signalment, survival, and prognostic factors in Doberman pinschers with end-stage cardiomyopathy. J Vet Intern Med 11:323, 1997
23. Calvert CA, Hall G, Jacobs G, et al. Clinical and pathologic findings in Doberman pinschers with occult car-

diomyopathy that died or developed congestive heart failure: 54 cases (1984–1991). J Am Vet Med Assoc 210:505, 1997
24. O'Grady MR, Horne R. Occult dilated cardiomyopathy: an echocardiographic and electrocardiographic study of 193 asymptomatic Doberman pinschers. Abstract. J Vet Intern Med 6:112, 1992
25. Harpster NK. Boxer cardiomyopathy: a review of the long-term benefits of antiarrhythmic therapy. Vet Clin North Am Small Anim Pract 21:989, 1991
26. Harpster NK. Boxer cardiomyopathy. *In* Kirk RW (ed): Kirk's Current Veterinary Therapy VIII. Philadelphia, WB Saunders, 1983, p 329
27. Tidholm A, Jönsson L. Dilated cardiomyopathy in the Newfoundland: a study of 37 cases (1983–1994). J Am Anim Hosp Assoc 32:465, 1996
28. Kittleson MD, Keene B, Pion PD, et al. Results of the Multicenter Spaniel Trial (MUST): taurine and carnitine-responsive dilated cardiomyopathy in American cocker spaniels with decreased plasma taurine concentration. J Vet Intern Med 11:204, 1997
29. Meurs KM, Spier AW, Miller MW, et al. Familial dysrhythmia is inherited as an autosomal dominant trait in selected boxer families. Abstract. J Vet Intern Med 12:199, 1998
30. Sandusky GE, Capen CC, Kerr KM, et al. Histological and ultrastructural evaluation of cardiac lesions in idiopathic cardiomyopathy in dogs. Can J Comp Med 48:81, 1984
31. Van Vleet JF, Ferrans VJ. Myocardial diseases of animals. Am J Pathol 124:98, 1986
32. Hazlett MJ, Maxie MG, Allen DG, et al. A retrospective study of heart disease in Doberman pinscher dogs. Can Vet J 24:205, 1983
33. McCarthy G. Idiopathic congestive cardiomyopathy of large breeds of dogs: observations on eleven cases. Irish Vet J 38:155, 1984
34. Thomas RE. Congestive cardiac failure in young cocker spaniels (a form of cardiomyopathy?): details of eight cases. J Small Anim Pract 28:265, 1987
35. Gooding JP, Robinson WF, Wyburn RS, et al. A cardiomyopathy in the English cocker spaniel: a clinico-pathological investigation. J Small Anim Pract 23:133, 1982
36. Staaden RV. Cardiomyopathy of English cocker spaniels. J Am Vet Med Assoc 178:1289, 1981
37. Katz AM. Membrane damage and the pathogenesis of cardiomyopathies. J Mol Cell Cardiol 17:11, 1985
37a. Tidholm A, Häggström J, Jönsson L. Prevalence of attenuated wavy fibers in myocardium of dogs with dilated cardiomyopathy. J Am Vet Med Assoc 212:1732, 1998.
38. Kasper EK, Agema WR, Hutchins GM, et al. The causes of dilated cardiomyopathy. J Am Coll Cardiol 23:586, 1994
39. Walker J (ed): The New Doberman Pinscher. New York, Howard Book House Inc, 1981
40. Day MJ. Inheritance of serum autoantibody, reduced serum IgA and autoimmune disease in a canine breeding colony. Vet Immunol Immunopathol 53:207, 1996
41. Michels VV, Moll PP, Miller FA, et al. The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy. N Engl J Med 326:77, 1992
42. Grunig E, Tasman JA, Kucherer H, et al. Frequency and phenotypes of familial dilated cardiomyopathy. J Am Coll Cardiol 31:186, 1988
43. Jones KJ, North KN. Recent advances in diagnosis of the childhood muscular dystrophies. J Paediatr Child Health 33:195, 1997
44. Towbin JA, Hejtmancik JF, Brink P, et al. X-linked dilated cardiomyopathy: molecular genetic evidence of linkage to the Duchenne muscular dystrophy (dystrophin) gene at the Xp21 locus. Circulation 87:1854, 1993
45. Muntoni F, Cau M, Ganau A, et al. Brief report: deletion of the dystrophin muscle-promoter region associated with X-linked dilated cardiomyopathy. N Engl J Med 329:921, 1993
46. Towbin JA. The role of cytoskeletal proteins in cardiomyopathies. Curr Opin Cell Biol 10:131, 1998
47. Kramer GA, Kittleson MD, Fox PR, et al. Plasma taurine concentrations in normal dogs and in dogs with heart disease. J Vet Intern Med 9:253, 1995
48. Pion PD, Kittleson MD, Rogers QR, et al. Myocardial failure in cats associated with low plasma taurine: a reversible cardiomyopathy. Science 237:764, 1987
49. Gavaghan BJ, Kittleson MD. Dilated cardiomyopathy in a cocker spaniel with taurine deficiency. Aust Vet J 75:862, 1997
50. Keene BW. Myocardial energy metabolism in dilated cardiomyopathy. Proceedings of the Fourth Annual Veterinary Medical Forum, 1986, p 9
51. Keene BW, et al. Frequency of myocardial carnitine deficiency associated with spontaneous canine dilated cardiomyopathy. Abstract. Proceedings of the Sixth Annual Veterinary Medical Forum, 1988, p 757
52. Keene BW, Kittleson MD, Rush JE, et al. Myocardial carnitine deficiency associated with dilated cardiomyopathy in Doberman pinschers. Abstract. J Vet Intern Med 3:126, 1989
53. Keene BW, Panciera DP, Atkins CE, et al. Myocardial L-carnitine deficiency in a family of dogs with dilated cardiomyopathy. J Am Vet Med Assoc 198:647, 1991
54. Keene BW. L-Carnitine supplementation in the therapy of canine dilated cardiomyopathy. Vet Clin North Am Small Anim Pract 21:1005, 1991
55. Keene BW. L-Carnitine deficiency in canine dilated cardiomyopathy. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 780
56. Regitz V, Shug AL, Fleck E. Defective myocardial carnitine metabolism in congestive heart failure secondary to dilated cardiomyopathy and to coronary, hypertensive and valvular heart disease. Am J Cardiol 65:755, 1990
57. Kawasaki N, Lee JD, Shimizu H, et al. Long-term L-carnitine treatment prolongs survival in rats with Adriamycin-induced heart failure. J Card Fail 2:293, 1996
58. Costa ND, Labuc RH. Case report: efficacy of oral carnitine therapy for dilated cardiomyopathy in boxer dogs. J Nutr 124(12 Suppl):2687S, 1994
59. Langsjoen PH, Folkers K. Long-term efficacy and safety of coenzyme Q10 therapy for idiopathic dilated cardiomyopathy. Am J Cardiol 65:521, 1990
60. Hofman-Bang C, Rehnqvist N, Swedberg K, et al. Coenzyme Q10 as an adjunctive in the treatment of chronic congestive heart failure. The Q10 Study Group. J Card Fail 1995 1:101
61. Archard LC, Bowles NE, Olsen EGJ, et al. Detection of persistent Coxsackie B virus RNA in dilated cardiomyopathy and myocarditis. Eur Heart J 8(suppl):437, 1987
62. Bowles NE, Rose ML, Taylor P, et al. End-stage dilated cardiomyopathy: persistence of enterovirus RNA in myocardium at cardiac transplantation and lack of immune response. Circulation 80:1128, 1989
63. Fallon JT. Myocarditis and dilated cardiomyopathy: different stages of the same disease? Cardiovasc Clin 18:155, 1988

64. Sole MJ, Liu P. Viral myocarditis: a paradigm for understanding the pathogenesis and treatment of dilated cardiomyopathy. J Am Coll Cardiol 22(suppl A):99A, 1993
65. Nho WG, Sur JH, Doster AR, et al. Detection of canine parvovirus in naturally infected dogs with enteritis and myocarditis by in situ hybridization. J Vet Diagn Invest 9:255, 1997
66. Lewis AB, Neustein HB, Takahashi M, et al. Findings on endomyocardial biopsy in infants and children with dilated cardiomyopathy. Am J Cardiol 55:143, 1985
67. Dec GW Jr, Palacios IF, Fallon JT, et al. Active myocarditis in the spectrum of acute dilated cardiomyopathies. N Engl J Med 312:885, 1985
68. Neumann DA, Burek CL, Baughman KL, et al. Circulating heart-reactive antibodies in patients with myocarditis or cardiomyopathy. J Am Coll Cardiol 16:839, 1990
69. Limas CJ, Goldenberg IF, Limas C. Autoantibodies against β-adrenoceptors in human idiopathic dilated cardiomyopathy. Circ Res 64:97, 1989
70. Limas CJ. Autoimmunity in dilated cardiomyopathy and the major histocompatibility complex. Int J Cardiol 54:113, 1996
71. Schulze K, Becker BF, Schauer R, et al. Antibodies to the ADP/ATP carrier—an autoantigen myocarditis and dilated cardiomyopathy—impair cardiac function. Circulation 81:959, 1990
72. Caforia ALP, Grazzini M, Mann JM, et al. Identification of α- and β-cardiac myosin heavy chain isoforms as major autoantigens in dilated cardiomyopathy. Circulation 85:1734, 1992
73. Cunningham MW, Antone SM, Gulizia JM, et al. Cytotoxic and viral neutralizing antibodies cross-react with streptococcal M protein, enteroviruses, and human cardiac myosin. Proc Natl Acad Sci USA 89:1320, 1992
74. Huber SA, Moraska A. Cytolytic T lymphocytes and antibodies to myocytes in Adriamycin-treated BALB/c mice. Evidence for immunity to drug-induced antigens. Am J Pathol 140:233, 1992
75. Limas CJ, Limas C. HLA antigens in idiopathic dilated cardiomyopathy. Br Heart J 62:379, 1989
76. Eckstein R, Mempel W, Bolte HD. Reduced suppressor cell activity in congestive cardiomyopathy and myocarditis. Circulation 65:1224, 1982
77. Sanderson JE, Koech D, Iha D, et al. T-lymphocyte subsets in idiopathic dilated cardiomyopathy. Am J Cardiol 55:755, 1985
78. O'Brien PJ, et al. Rapid ventricular pacing of dogs to heart failure: biochemical and physiological studies. Can J Physiol Pharmacol 68:34, 1990
79. O'Brien PJ, O'Grady MR, Lumsden JH, et al. Clinical pathologic profiles of dogs and turkeys with congestive heart failure, either noninduced or induced by rapid ventricular pacing, and turkeys with furazolidone toxicosis. Am J Vet Res 54:60, 1993
80. Armstrong PW, Stopps TP, Ford SE, et al. Rapid ventricular pacing in the dog: pathophysiological studies of heart failure. Circulation 74:1075, 1986
81. Redfield MM, Aarhus LL, Wright RS, et al. Cardiorenal and neurohumoral function in a canine model of early left ventricular dysfunction. Circulation 87:2016, 1993
82. Spinale FG, Grine RC, Tempel GE, et al. Alterations in the myocardial capillary vasculature accompany tachycardia-induced cardiomyopathy. Basic Res Cardiol 87:65, 1992
83. Kajstura J, Zhang X, Liu Y, et al. The cellular basis of pacing-induced dilated cardiomyopathy. Myocyte cell loss and myocyte cellular reactive hypertrophy. Circulation 92:2306, 1995
84. Ravens U, Davis K, Davies CH, et al. Tachycardia-induced failure alters contractile properties of canine ventricular myocytes. Cardiovasc Res 32:613, 1996
85. Grogan M, Smith HC, Gersh BJ, et al. Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy. Am J Cardiol 69:1570, 1992
86. Zupan I, Rakovec P, Budihna N, et al. Tachycardia-induced cardiomyopathy in dogs; relation between chronic supraventricular and chronic ventricular tachycardia. Int J Cardiol 56:75, 1996
87. Atkins CE, Kanter R, Wright K, et al. Orthodromic reciprocating tachycardia and heart failure in a dog with a concealed posteroseptal accessory pathway. J Vet Intern Med 9:43, 1995
88. Neubauer S, Krahe T, Schindler R, et al. ^{31}P magnetic resonance spectroscopy in dilated cardiomyopathy and coronary artery disease: altered cardiac high-energy phosphate metabolism in heart failure. Circulation 86:1810, 1992
89. Ferrans VJ. Pathologic anatomy of the dilated cardiomyopathies. Am J Cardiol 64:9C, 1989
90. Urie PM, Billingham ME. Ultrastructural features of familial cardiomyopathy. Am J Cardiol 62:325, 1988
91. Ades LC, Gedeen AK, Wilson MJ, et al. Barth syndrome: clinical features and confirmation of gene localization to distal Xq28. Am J Med Genet 45:327, 1993
92. Bolhuis PA, Hensels GW, Hulsebos TJ, et al. Mapping of the locus for X-linked cardioskeletal myopathy with neutropenia and abnormal mitochondria (Barth syndrome) to Xq28. Am J Hum Genet 48:481, 1991
93. O'Brien PJ. Deficiencies of myocardial tropinin-T and creatine kinase MB isoenzyme in dogs with idiopathic dilated cardiomyopathy. Am J Vet Res 58:11, 1997
94. O'Brien PJ, O'Grady M, McCutcheon LH, et al. Myocardial myoglobin deficiency in various animal models of congestive heart failure. J Mol Cell Cardiol 24:721, 1992
95. McCutcheon L, Cory CR, Norwack L, et al. Respiratory chain defect of mitochondria in idiopathic dilated cardiomyopathy of Doberman pinscher dogs. Can J Pharmacol 70:1529, 1992
96. Figueredo VM, Camacho SA. Basic mechanisms of myocardial dysfunction: cellular pathophysiology of heart failure. Curr Opin Cardiol 8:369, 1993
97. Lorrell BH. Significance of diastolic dysfunction of the heart. Annu Rev Med 42:411, 1991
98. Beuckelmann DJ, Nabauer M, Erdmann E. Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. Circulation 85:1046, 1992
99. Bailey BA, Houser SR. Calcium transients in feline left ventricular myocytes with hypertrophy induced by slow progressive pressure overload. J Mol Cell Cardiol 24:365, 1992
100. Perreault CL, Shannon RP, Komamura K, et al. Abnormalities in intracellular calcium regulation and contractile function in myocardium from dogs with pacing-induced heart failure. J Clin Invest 89:932, 1992
101. Bouron A, Potreau D, Raymond G. The L-type calcium current in single hypertrophied cardiomyocytes isolated from the right ventricle of the ferret heart. Cardiovasc Res 26:662, 1992
102. Takahashi T, Allen PD, Lacro RV, et al. Expression of dihydropyridine receptor (Ca^{2+} channel) and calsequestrin genes in the myocardium of patients with end-stage heart failure. J Clin Invest 90:925, 1992
103. D'Agnolo A, Luciani GB, Mazzucco A, et al. Contractile properties of Ca^{2+} release activity of the sarcoplasmic

reticulum in dilated cardiomyopathy. Circulation 85:518, 1992
104. Cory CR, Shen H, O'Brien PJ. Compensatory asymmetry in down-regulation and inhibition of the myocardial Ca^{2+} cycle in congestive heart failure produced in dogs by idiopathic dilated cardiomyopathy and rapid ventricular pacing. J Mol Cell Cardiol 26:173, 1994
105. Feldman AM, Tena RG, Kessler PD, et al. Diminished β-adrenergic responsiveness and cardiac dilation in hearts of myopathic Syrian hamsters (BIO 53.58) are associated with a functional abnormality of the G stimulatory protein. Circulation 81:1341, 1990
106. Bristow MR, Anderson FL, Port JD, et al. Differences in β-adrenergic neuroeffector mechanisms in ischemic versus idiopathic dilated cardiomyopathy. Circulation 84:1024, 1991
107. Neumann J, Schmitz W, Scholz H, et al. Increase in myocardial G_i proteins in heart failure. Lancet 2:936, 1988
108. Figueredo VM, Brandes R, Weiner MW, et al. Cardiac contractile dysfunction during mild coronary flow reductions is due to an altered calcium-pressure relationship in rat hearts. J Clin Invest 90:1794, 1992
109. Camacho SA, Figueredo VM, Brandes R, et al. Calcium-dependent fluorescence transients and phosphate metabolism during low flow ischemia in isolated rat hearts. Am J Physiol 265:H114, 1993
110. Hoey A. Canine dilated cardiomyopathy—are there defects at the receptor level? Abstract. Proceedings, British Small Anim Veterinary Medical Association, 1991, p 142
111. Gilbert SJ, Wotton PR, Tarlton JF, et al. Increased expression of promatrix metalloproteinase-9 and neutrophil elastase in canine dilated cardiomyopathy. Cardiovasc Res 34:377, 1997
112. Bonagura JD, Ware WA. Atrial fibrillation in the dog: clinical findings in 81 cases. J Am Anim Hosp Assoc 22:111, 1986
113. Naito M. The hemodynamic consequences of cardiac arrhythmias: evaluation of the relative roles of abnormal atrioventricular sequencing, irregularity of ventricular rhythm, and atrial fibrillation in a canine model. Am Heart J 106:284, 1983
114. Darke PGG. An evaluation of cardiac dysrhythmias by Doppler echocardiography. Proceedings of the Tenth Annual Veterinary Medical Forum, 1992, p 602
115. Fruhwald FM, Dusleag J, Eber B, et al. Long-term outcome and prognostic factors in dilated cardiomyopathy. Preliminary results. Angiology 45:763, 1994
116. Calvert CA. Update: canine dilated cardiomyopathy. *In* Kirk RW, Bonagura JD (eds): Kirk's Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 773
117. Reddy PS. The third heart sound. Int J Cardiol 7:213, 1985
118. Butman SM, Ewy GA, Standen JR, et al. Bedside cardiovascular examination in patients with severe chronic heart failure: importance of rest or inducible jugular venous distension. J Am Coll Card 22:968, 1993
119. Kono T, Rosman H, Alam M, et al. Hemodynamic correlates of the third heart sound during evolution of chronic heart failure. J Am Coll Cardiol 21:419, 1993
120. Calvert CA, Jacobs GJ, Pickus CW. Bradycardia-associated episodic weakness, syncope, and aborted sudden death in cardiomyopathic Doberman pinschers. J Vet Intern Med 10:88, 1996
121. O'Brien PB, O'Grady MR, Lumsden JH, et al. Clinical pathologic profiles of dogs and turkeys with congestive heart failure, either noninduced or induced by rapid ventricular pacing, and turkeys with furazolidone toxicosis. Am J Vet Res 54:60, 1993
122. Lumsden JH, O'Grady MR, Johnstone IB, et al. Prevalence of hypothyroidism and von Willebrand's disease in Doberman pinschers, and the observed relationship between thyroid, von Willebrand, and cardiac status. Abstract. J Vet Intern Med 7:115, 1993
123. Calvert CA, Chapman WL, Toal RL. Congestive cardiomyopathy in Doberman pinscher dogs. J Am Vet Med Assoc 181:598, 1982
124. Connolly SJ, Cairns JA, on behalf of the CAMIAT pilot study group: Comparison of one-, six- and 24-hour ambulatory electrocardiographic monitoring for ventricular arrhythmia as a predictor of mortality in survivors of acute myocardial infarction. Am J Cardiol 69:308, 1992
125. Hasslick MJ, Maxie MG, Allen DG, et al. A retrospective study of heart disease in Doberman pinscher dogs. Can Vet J 24:205, 1983
126. O'Grady MR, Horne R. Outcome of 103 asymptomatic Doberman pinschers: incidence of dilated cardiomyopathy in a longitudinal study. Abstract. J Vet Intern Med 9:199, 1995
127. Calvert CA. Long-term ambulatory electrocardiographic monitoring in the diagnosis of occult cardiomyopathy in Doberman pinschers. Proceedings, Annual Meeting, American College of Veterinary Internal Medicine, 1991, p 691
128. Calvert CA, Brown J. Use of M-mode echocardiography in the diagnosis of congestive cardiomyopathy in Doberman pinschers. J Am Vet Med Assoc 189:293, 1986
129. Atkins CE, Snyder PS. Systolic time intervals and their derivatives for evaluation of cardiac function. J Vet Intern Med 6:55, 1992
130. Darke GG. Doppler echocardiography in canine congestive cardiomyopathy. Proceedings of the Eleventh Annual Veterinary Medical Forum, 1993, p 531
131. Bennet ED. Ascending aortic blood velocity and acceleration using Doppler ultrasound in the assessment of left ventricular function. Cardiovasc Res 18:632, 1984
132. Brown KK. Noninvasive evaluation of ventricular ejection dynamics in dogs. Proceedings of the Tenth Annual Veterinary Medical Forum, 1992, p 613
133. Werner GS, Schaefer C, Dirks R, et al. Doppler echocardiographic assessment of left ventricular filling in idiopathic dilated cardiomyopathy during a one-year follow-up: relation to the clinical course of disease. Am Heart J 126:1408, 1993
134. Calvert CA. Diagnosis and therapy of occult cardiomyopathy. Proceedings, XVI World Veterinary Congress, 1991, p 27
135. Smucker ML, Kaul S, Woodfield JA, et al. Naturally occurring cardiomyopathy in the Doberman pinscher: a possible large animal model of human cardiomyopathy. J Am Coll Cardiol 16:200, 1990
136. O'Grady MR, Horne R. Occult dilated cardiomyopathy: echocardiographic and electrocardiographic findings in 192 asymptomatic Doberman pinschers. J Vet Intern Med (in press)
137. O'Grady MR, Horne R. Echocardiographic findings in 51 normal Doberman pinschers. Abstract. J Vet Intern Med 9:202, 1995
138. O'Grady M, Horne R. Prevalence of dilated cardiomyopathy in Doberman pinschers: a 4.5-year follow-up. Abstract. J Vet Intern Med 12:199, 1998
139. Sisson D. Evidence for or against the efficacy of afterload reducers for management of heart failure in dogs. Vet Clin North Am Small Anim Pract 21:945, 1991
140. Unverferth DV, Blanford M, Kates RE, et al. Tolerance

to dobutamine after a 72-hour continuous infusion. Am J Med 69:262, 1980
141. Smith CJ, Huang R, Sun D, et al. Development of decompensated dilated cardiomyopathy is associated with decreased gene expression and activity of the milrinone-sensitive cAMP phosphodiesterase PDE3A. Circulation 96:3116, 1997
142. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 325:293, 1991
143. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 325:303, 1991
144. The CONSENSUS Trail Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the cooperative North Scandinavian enalapril survival study (CONSENSUS). N Engl J Med 316:1429, 1987
145. Pfeffer MA, Braunwald E, Moye LA, et al. The effect of captopril on mortality and morbidity in patients with left ventricular dysfunction following myocardial infarction: results of the survival and ventricular enlargement (SAVE) trial. N Engl J Med 327:669, 1992
146. Fox PR, Sisson DD. Angiotensin-converting enzyme inhibitors. *In* Bonagura JD (ed): Kirk's Current Veterinary Therapy XII. Small Animal Practice. Philadelphia, WB Saunders, 1995, p 786
147. The IMPROVE Study Investigators. Clinical effects of enalapril maleate in dogs with naturally acquired heart failure: results of the invasive multicenter prospective veterinary evaluation of enalapril. J Vet Intern Med 9:234, 1995
148. Hofmann S, Kersten U. The effectiveness and tolerance of ramipril in comparison to captopril for heart failure in dogs. Dtsch Tierarztl Wochenschr 103:159, 1996
149. Morisse B, Kersten U. Treatment of heart failure in dogs with ACE inhibitors: comparison of quinapril and captopril. Tierarztl Prax 23:489, 1995
150. Pouchelon JL, and the Benazepril Veterinary Investigators: Treatment of heart failure in dogs with benazepril—results of European double-blind placebo controlled study. Abstract. J Vet Intern Med 10:163, 1996
151. Kittleson MD. The acute hemodynamic effects of captopril in dogs with heart failure. J Vet Pharmacol Ther 16:1, 1993
152. Packer M, O'Connor CM, Ghali JK. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. N Engl J Med 335:1107, 1996
153. Knight DH. Efficacy of inotropic support of the failing heart. Vet Clin North Am Small Anim Pract 21:879, 1991
154. Kittleson MD, Eyster GE, Knowlen GG, et al. Efficacy of digoxin administration in dogs with idiopathic congestive cardiomyopathy. J Am Vet Med Assoc 186:162, 1985
155. Uretsky BF, Young JB, Shahidi FE, et al for the PROVED Investigative Group. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. J Am Coll Cardiol 22:955, 1993
156. Arnold SB, Byrd RC, Meister W, et al. Long-term digitalis therapy improves left ventricular function in heart failure. N Engl J Med 303:1443, 1980
157. DiBianco R, Shabetai R, Kosta KW, et al, for the Milrinone Multicenter Trial Group. A comparison of oral milrinone, digoxin, and their combinations in the treatment of patients with chronic heart failure. N Engl J Med 320:677, 1989
158. The Digoxin Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 336:525, 1997
159. Ferguson DW, Berg WJ, Sanders JS, et al. Sympathoinhibitory responses to digitalis glycosides in heart failure patients: direct evidence from sympathetic neural recordings. Circulation 80:65, 1989
160. Hamlin RL. Therapy of supraventricular tachycardia and atrial fibrillation. *In* Kirk RW, Bonagura JD (eds): Kirk's Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 745
161. Hamlin RL. Clinical use of diltiazem in atrial fibrillation. Abstract. Proceedings, 6th Annual Veterinary Medicine Forum, ACVIM, 1988, p 759
162. Waagstein F, Bristow MR, Swedberg K, et al for the Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Lancet 342:1441, 1993
163. Gottlieb SS. β-Blockers for heart failure: where are we now? Curr Opin Cardiol 9:295, 1994
164. CAST Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 321:406, 1989
165. CAST Investigators. Failure of treatment with moricizine to improve survival in a randomized trial of arrhythmia suppression after myocardial infarction (MI): The Cardiac Arrhythmia Suppression Trial (CAST). Abstract. J Am Coll Cardiol 19:199A, 1992
166. Echt DS, Leibson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide or placebo. N Engl J Med 324:781, 1991
167. Zipes DP. Specific arrhythmias: diagnosis and treatment. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB Saunders, 1994, p 667
168. Calvert CA, Pickus CW, Jacobs GJ. Efficacy and toxicity of tocainide for the treatment of ventricular tachyarrhythmias in Doberman pinschers with occult cardiomyopathy. J Vet Intern Med 10:235, 1996
169. Garg R, Yusuf S. Current and ongoing randomized trails in heart failure and left ventricular dysfunction. J Am Coll Cardiol 22(suppl A):194A, 1993
170. Ishida S, Makino N, Masutomo K, et al. Effect of metoprolol on the β-adrenoceptor density of lymphocytes in patients with dilated cardiomyopathy. Am Heart J 125:1311, 1993
171. Heilbrun SM, Shah P, Bristow MR, et al. Increased β-receptor density and improved hemodynamic response to catecholamine stimulation during long-term metoprolol therapy in heart failure from dilated cardiomyopathy. Circulation 79:483, 1989
172. Olsen SL, Yanowitz FG, Gilbert EM, et al. Beta-blocker related improvement in submaximal exercise tolerance in heart failure from idiopathic dilated cardiomyopathy. Abstract. J Am Coll Cardiol 19:146A, 1992
173. Waagstein F, Hjalmarson A, Varnauskas E, et al. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. Br Heart J 37:1022, 1975
174. Heilbrun SM, Shah P, Bristow MR, et al. Increased β-receptor density and improved hemodynamic response to catecholamine stimulation during long-term metoprolol therapy in heart failure from dilated cardiomyopathy. Circulation 79:483, 1989
175. Eichhorn EJ, Heesch CM, Barnett JH, et al. Effect of

metoprolol on myocardial function and energetics in patients with nonischemic dilated cardiomyopathy: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol 24:1310, 1994
176. Bristow MR. Pathophysiologic and pharmacologic rationales for clinical management of chronic heart failure with beta-blocking agents. Am J Cardiol 71:12C, 1993
177. Waagstein F, Bristow MR, Swedberg K, et al for the Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Lancet 342:1441, 1993
178. CIBIS Investigators and Committees. A randomized trial of β-blockade in heart failure: the cardiac insufficiency bisoprolol study (CIBIS). Circulation 90:1765, 1994
179. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 334:1349, 1996
180. Unverferth DV, Magorien RD, Lewis RP, et al. Long-term benefit of dobutamine in patients with congestive cardiomyopathy. Am Heart J 100:622, 1980
181. Feldman AM, Bristow MR, Parmley WW, et al. Effects of vesnarinone on morbidity and mortality in patients with heart failure. N Engl J Med 329:149, 1993
182. Kubo SH, Gollub S, Bourge R, et al for the Pimobendan Multicenter Research Group. Beneficial effects of pimobendan on exercise tolerance and quality of life in patients with heart failure: results of a multicenter trial. Circulation 85:942, 1992
183. O'Connel JB, Breen TJ, Hosenpud JD. Heart transplantation in dilated heart muscle disease and myocarditis. Eur Heart J 16(Suppl O):137, 1996
184. Chiu RCJ, Odim JNK, Burgess JH, and the McGill Cardiomyoplasty Group. Responses to dynamic cardiomyoplasty for idiopathic dilated cardiomyopathy. Am J Cardiol 72:475, 1993
185. Orton EC, Monnet E, Brevard SM, et al. Dynamic cardiomyoplasty for treatment of idiopathic dilatative cardiomyopathy in a dog. J Am Vet Med Assoc 205:1415, 1994
186. White RN, Cobb MA, Brownlie SE. Skeletal muscle extra-aortic counterpulsation in dogs with dilated cardiomyopathy. J Small Anim Pract 38:554, 1997
187. Brecker SJD, Xiao HB, Sparrow J, et al. Effects of dual-chamber pacing with short atrioventricular delay in dilated cardiomyopathy. Lancet 340:1308, 1992
188. Gordon SG, O'Grady MO, Tully L, et al. Assessment of the ability of physiologic dual chambered pacing to improve left ventricular performance in Doberman pinschers with stable congestive heart failure due to dilated cardiomyopathy: an acute study. Abstract. J Vet Intern Med 12:239, 1998
189. Stevenson LW, Tillisch JH, Hamilton M, et al. Importance of hemodynamic response to therapy in predicting survival with ejection fraction < 20% secondary to ischemic or nonischemic dilated cardiomyopathy. Am J Cardiol 66:1348, 1990
190. Lamontagne J, DiFruscia R. Cardiomyopathie dilatee canine: la survie apres le diagnostic. Med Vet Quebec 21:141, 1991
191. Franciosa JA, Wilen M, Ziesche S, et al. Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. Am J Cardiol 51:831, 1983
192. Liu S-K, Maron BJ, Tilley LP, et al. Canine hypertrophic cardiomyopathy. J Am Vet Med Assoc 174:708, 1979
193. Liu S-K, Maron BJ, Tilley LP, et al. Hypertrophic cardiomyopathy in the dog. Am J Pathol 94:497, 1979
194. Yamada E. A canine case of hypertrophic cardiomyopathy. J Jpn Vet Med Assoc 36:12, 1983
195. Thomas WP, Mathewson JW, Suter PF, et al. Hypertrophic obstructive cardiomyopathy in a dog: clinical, hemodynamic, angiographic, and pathologic studies. J Am Anim Hosp Assoc 20:253, 1984
196. Swindle MM, Huber AC, Ran JS, et al. Mitral valve prolapse and hypertrophic cardiomyopathy in a pup. J Am Vet Med Assoc 184:1515, 1984
197. Marks CA. Hypertrophic cardiomyopathy in a dog. J Am Vet Med Assoc 203:1020, 1993
198. Sisson DD. Heritability of idiopathic myocardial hypertrophy and dynamic subaortic stenosis in pointer dogs. Abstract. J Vet Intern Med 4:118, 1990
199. Maron BJ, Tilley LP, Liu SK, et al. Spontaneously occurring hypertrophic cardiomyopathy in dogs and cats: a potential animal model of a human disease. *In* Kaltenbach M, Epstein SE (eds): Hypertrophic Cardiomyopathy. New York, Springer-Verlag, 1982, p 73
200. Liu SK, Roberts WC, Maron BJ. Comparison of morphologic findings in spontaneously occurring hypertrophic cardiomyopathy in humans, cats and dogs. Am J Cardiol 72:944, 1993
201. Sisson DD. Fixed and dynamic subvalvular aortic stenosis in dogs. *In* Kirk RW, Bonagura JD (eds): Kirk's Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 760
202. Sisson D, Thomas WP. Dynamic subaortic stenosis in a dog with congenital heart disease. J Am Anim Hosp Assoc 20:657, 1984
203. Levine RA, Vlahakes GJ, Lefebvre X, et al. Papillary muscle displacement causes systolic anterior motion of the mitral valve. Experimental validation and insights into the mechanism of subaortic obstruction. Circulation 15:1189, 1995
204. Maron BJ. Asymmetry in hypertrophic cardiomyopathy: the septal to free wall thickness ratio revisited. Am J Cardiol 55:835, 1985
205. Klues HG, Maron BJ, Dollar AL, et al. Diversity of structural mitral valve alterations in hypertrophic cardiomyopathy. Circulation 85:1651, 1992
206. Mikami T, Hashimoto M, Kudo T, et al. Mitral valve and its ring in hypertrophic cardiomyopathy—a mechanism creating surplus mitral leaflet involved in systolic anterior motion. Jpn Circ J 52:597, 1988
207. Muna FT, Ferrans VJ, Pierce JE, et al. Discrete subaortic stenosis in Newfoundland dogs: association of infective endocarditis. Am J Cardiol 41:746, 1978
208. Buoscio DA, Sisson D, Zachary J. Clinical and pathologic characterization of an unusual form of subvalvular aortic stenosis in four golden retriever dogs. J Am Anim Hosp Assoc 30:100, 1994
209. Conte MR, Bongioanni S, Dall'Orto G, et al. Fixed subaortic stenosis associated with hypertrophic cardiomyopathy: report of a rare familial occurrence. G Ital Cardiol 28:53, 1998
210. Kimura A, Harada H, Park JE, et al. Mutations in the cardiac troponin I gene associated with hypertrophic cardiomyopathy. Nat Genet 16:379, 1997
211. Silvestri G, Bertini E, Servidei S, et al. Maternally inherited cardiomyopathy: a new phenotype associated with the A to G AT nt.3243 of mitochondrial DNA (MELAS mutation). Muscle Nerve 20:221, 1997
212. Bright JM, Golden AL. Evidence for or against efficacy of calcium channel blockers for management of hypertrophic cardiomyopathy in cats. Vet Clin North Am Small Anim Pract 21:1023, 1991
213. Wigle ED. Novel insights into the clinical manifestations and treatment of hypertrophic cardiomyopathy. Curr Opin Cardiol 10:299, 1995

214. Pasipoularides A. Clinical assessment of ventricular ejection dynamics with and without outflow obstruction. J Am Coll Cardiol 15:859, 1990
215. Leachman RD. Potential mechanisms of improvement after various treatments for hypertrophic obstructive cardiomyopathy. Tex Heart Inst J 22:126, 1995
216. Fox PR. Evidence for or against efficacy of beta-blockers and aspirin for management of feline cardiomyopathies. Vet Clin North Am Small Anim Pract 21:1011, 1991
217. Cooke KL, Snyder PS. Calcium channel blockers in veterinary medicine. J Vet Med Assoc 12:123, 1998
218. McAreavey D, Fananapazir L. Altered cardiac hemodynamic and electrical state in normal sinus rhythm after chronic dual-chamber pacing for relief of left ventricular outflow obstruction in hypertrophic cardiomyopathy. Am J Cardiol 70:651, 1992
219. Guize L, Gras D, Jeanrenaud X. Pacing in hypertrophic obstructive cardiomyopathy. A randomized cross-over study. PIC Study Group. Eur Heart J 18:1249, 1997
220. Cohn LH, Trehan H, Collins JJ Jr, et al. Long-term follow-up of patients undergoing myotomy/myectomy for obstructive hypertrophic cardiomyopathy. Am J Cardiol 70:657, 1992
221. Fananapazir L, Cannon RO 3d, Tripodi D, et al. Impact of dual-chamber permanent pacing in patients with obstructive hypertrophic cardiomyopathy with symptoms refractory to verapamil and beta-adrenergic blocker therapy. Circulation 85:2149, 1992
222. Di Mario C, Musso P, Moses JJ. Alcoholization of the interventricular septum (Sigwart procedure) for treatment of hypertrophic cardiomyopathy. G Ital Cardiol 28:45, 1998
223. Primo J, Geelen P, Brugada J. Hypertrophic cardiomyopathy: role of the implantable cardioverter-defibrillator. J Am Coll Cardiol 31:1081, 1998
224. Michalak M, Opas M. Functions of dystrophin and dystrophin-associated proteins. Curr Opin Neurol 10:436, 1997
225. Brown RH Jr. Dystrophin-associated proteins and the muscular dystrophies. Annu Rev Med 48:457, 1997
226. Valentine BA, Winand NJ, Pradham D, et al. Canine X-linked muscular dystrophy as an animal model of Duchenne muscular dystrophy: a review. Am J Med Genet 42:352, 1992
227. Valentine BA, Cummings JF, Cooper BJ, et al. Development of Duchenne-type cardiomyopathy: morphologic studies in a canine model. Am J Pathol 135:671, 1989
228. Moise NS, Valentine BA, Brown CA, et al. Duchenne's cardiomyopathy in a canine model: electrocardiographic and echocardiographic studies. J Am Coll Cardiol 17:812, 1991
229. Howell JM, Fletcher S, Kakulas BA, et al. Use of the dog model for Duchenne muscular dystrophy in gene therapy trials. Neuromusc Disord 7:325, 1997
230. Miller MS, Tilley LP, Atkins CE. Persistent atrial standstill (atrioventricular muscular dystrophy). *In* Kirk RW, Bonagura JD (eds): Kirk's Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 786
231. Jeraj K, Ogburn PN, Edwards WD, et al. Atrial standstill, myocarditis and destruction of cardiac conduction system: clinicopathologic correlation in a dog. Am Heart J 99:185, 1980
232. Kubo S, Tsukahara T, Arahata K. [Emery-Dreifuss muscular dystrophy]. Nippon Rinsho 55:3186, 1997
233. Cartegni L, di Barletta MR, Barresi R, et al. Heart-specific localization of emerin: new insights into Emery-Dreifuss muscular dystrophy. Hum Mol Genet 6:2257, 1997
234. Brown RH Jr. Dystrophin-associated proteins and the muscular dystrophies. Annu Rev Med 48:457, 1997
235. van der Kooi AJ, de Voogt WG, Barth PG, et al. The heart in limb-girdle muscular dystrophy. Heart 79:73, 1998
236. Corrado D, Basso C, Thiene G, et al. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. J Am Coll Cardiol 30:1512, 1997
237. Simpson KW, Bonagura JD, Eaton KA. Right ventricular cardiomyopathy in a dog. J Vet Intern Med 8:306, 1994
238. Bright JM, McEntee M: Isolated right ventricular cardiomyopathy in a dog. J Am Vet Med Assoc 207:64, 1995
239. Gwathmey JK, Davidoff AJ. Pathophysiology of cardiomyopathies: Part II. Drug-induced and other interventions. Curr Opin Cardiol 9:369, 1994
240. Van Vleet JF, Ferrans VJ, Weirich WE. Cardiac diseases induced by chronic Adriamycin administration in dogs and an evaluation of vitamin E and selenium as cardioprotectants. Am J Pathol 99:13, 1980
241. Kehoe R, Kehoe R, Singer DH, et al. Adriamycin-induced cardiac dysrhythmias in an experimental dog model. Cancer Treat Rep 62:963, 1978
242. Loar AS, Susaneck SJ. Doxorubicin-induced cardiotoxicity in five dogs. Semin Vet Med Surg 1:68, 1986
243. Mauldin GE, Smith GE, Matus RE, et al. Doxorubicin-induced cardiotoxicosis—clinical features in 32 dogs. J Vet Intern Med 6:82, 1992
244. Page RL, Keene BW. Doxorubicin cardiomyopathy. *In* Kirk RW, Bonagura JD (eds): Kirk's Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 783
245. Hahn KA, Hahn EA. Epirubicin (4′-epi-doxorubicin) chemotherapy. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI: Small Animal Practice. Philadelphia, WB Saunders, 1992, p 392
246. Ogilvie GK, Moore AS. Mitoxantrone. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI: Small Animal Practice. Philadelphia, WB Saunders, 1992, p 399
247. Appelbaum FR, Strauchen JA, Graw RG. Acute, lethal carditis caused by high-dose combination chemotherapy. Lancet 1:58, 1976
248. Unverferth DV, Magorien RD, Balcerzak SP, et al. Early changes in human myocardial nuclei after doxorubicin. Cancer 52:215, 1983
249. Schwartz RG, McKenzie WB, Alexander J, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. Am J Med 82:1109, 1987
250. Shulman LN, Braunwald E, Rosenthal DS. Hematological-oncological disorders and heart disease. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, 5th ed. Philadelphia, WB Saunders, 1997, p 1786
251. Price GS, Page RL, Fischer BM, et al. Efficacy and toxicity of doxorubicin/cyclophosphamide maintenance therapy in dogs with multicentric lymphosarcoma. J Vet Intern Med 5:259, 1991
252. Berg J, Weinstein MJ, Springfield DS, et al. Results of surgery and doxorubicin chemotherapy in dogs with osteosarcoma. J Am Vet Med Assoc 206:1555, 1995
253. Imondi AR, Della Torre P, Mazue G, et al. Dose-response relationship of dexrazoxane for prevention of doxorubicin-induced cardiotoxicity in mice, rats, and dogs. Cancer Res 56:4200, 1996
254. Walvoort HC, van Nes JJ, Stokhof AA, et al. Canine glycogen storage disease type II: a clinical study of

four affected Lapland dogs. J Am Anim Hosp Assoc 20:279, 1984
255. Mostafa IE. A case of glycogenic cardiomegaly in a dog. Acta Vet Scand 11:197, 1970
256. DeFrancesco TC, Atkins CE, Keene BW. Myocardial infarction complicating management of congestive heart failure in a dog. J Am Anim Hosp Assoc 32:68, 1996
257. Liu SK, Fox PR. Myocardial ischemia and infarction. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 791
258. Bjotvedt G, Howard EB. Acute myocardial infarction in a racing greyhound. Canine Pract 10:24, 1983
259. Liu S-K, Tilley LP, Tappe JP, et al. Clinical and pathologic findings in dogs with atherosclerosis; 21 cases (1970–1983). J Am Vet Med Assoc 189:227, 1986
260. King JM, Roth L, Haschek WM, et al. Myocardial necrosis secondary to neural lesions in domestic animals. J Am Vet Med Assoc 180:144, 1982
261. Pinson DM. Myocardial necrosis and sudden death after an episode of aggressive behavior in a dog. J Am Vet Med Assoc 211:1371, 1997
262. Hayes MA, Russel RG, Babiuk LA. Sudden death in young dogs with myocarditis caused by parvovirus. J Am Vet Med Assoc 174:1197, 1979
263. Carpenter JL, Roberts RM, Harpster NK. Intestinal and cardiopulmonary forms of parvovirus infection in a litter of pups. J Am Vet Med Assoc 176:1269, 1980
264. Gagnon AN, Crowe SP, Allen DG, et al. Myocarditis in puppies: clinical, pathological and virological findings. Can Vet J 21:195, 1980
265. Lenghaus C, Studdert MJ. Generalized parvovirus disease in neonatal pups. J Am Vet Med Assoc 181:41, 1982
266. Jezyk PF, Haskins ME, Jones CL. Myocarditis of probable viral origin in pups of weaning age. J Am Vet Med Assoc 174:1204, 1979
267. Robinson WF, Huxtable CR, Pass DA. Canine parvovirus myocarditis. A morphologic description of the natural disease. Vet Pathol 17:282, 1980
268. Lenghaus C, Studdert MJ. Animal model of human disease: acute and chronic viral myocarditis; acute, diffuse nonsuppurative active myocarditis and residual myocardial scarring following infection with canine parvovirus. Am J Pathol 115:316, 1984
269. Kramer JM, Meunier PC, Pollock RVH. Canine parvovirus update. VM/SAC 75:1541, 1980
270. Atwell RB, Kelly WR. Canine parvovirus: a cause of chronic myocardial fibrosis and adolescent congestive heart failure. J Small Anim Pract 21:609, 1980
271. Thomas RE. Canine idiopathic congestive cardiomyopathy: breed incidence from a series of 17 cases. Vet Rec 121:423, 1987
272. Higgins RJ, Krakowka S, Metzler AE, et al. Canine distemper virus–associated cardiac necrosis in the dog. Vet Pathol 18:472, 1981
273. Carmichael LE, Greene CE. Canine herpesvirus infection. *In* Greene CE (ed): Infectious Diseases of the Dog and Cat. Philadelphia, WB Saunders, 1990, p 252
274. Williams GD, Adams LG, Yaeger RG, et al. Naturally occurring trypanosomiasis (Chagas' disease) in dogs. J Am Vet Med Assoc 171:171, 1977
275. Tomlinson MJ, Chapman WL, Hanson WL. Occurrence of antibody to *Trypanosoma cruzi* in dogs in the southeastern U.S. Am J Vet Res 42:1444, 1981
276. Tippit TS. Canine trypanosomiasis (Chagas' disease). Southwest Vet 31:97, 1978
277. Snider TG, Yaeger RG, Dellucky J. Myocarditis caused by *Trypanosoma cruzi* in a native Louisiana dog. J Am Vet Med Assoc 177:247, 1980
278. Blandon R, Leandro IM, Johnson CM. Clinical, echocardiographic, and angiographic evaluation of natural reservoirs of Chagas' disease in the Republic of Panama. Rev Med Panama 20:108, 1995
279. Barr SC, Gossett KA, Klei TR, et al. Clinical, clinicopathologic, and parasitologic observations of trypanosomiasis in dogs infected with North American *Trypanosoma cruzi* isolates. Am J Vet Res 52:954, 1991
280. Barr SC, Schmidt SP, Brown CC, et al. Pathologic features of dogs inoculated with North American *Trypanosoma cruzi* isolates. Am J Vet Res 52:2033, 1991
281. Andrade ZA, Andrade SG, Sadgursky M, et al. Damage and healing in the conducting system of the heart (an experimental study of dogs infected with *Trypanosoma cruzi*). J Pathol 143:93, 1984
282. Barr SC, Simpson RM, Schmidt SP, et al. Chronic dilatative myocarditis caused by *Trypanosoma cruzi* in two dogs. J Am Vet Med Assoc 195:1237, 1989
283. Dubey JP, Greene CE, Lappin MR. Toxoplasmosis and neosporosis. *In* Greene CE (ed): Infectious Diseases of the Dog and Cat. Philadelphia, WB Saunders, 1990, p 818
284. Odin M, Dubey JP. Sudden death associated with *Neospora caninum* myocarditis in a dog. J Am Vet Med Assoc 203:831, 1993
285. Barber JS, Trees AJ. Clinical aspects of 27 cases of neosporosis in dogs. Vet Rec 2:439, 1996
286. Hay WH, Shell LG, Lindsay DS, et al. Diagnosis and treatment of *Neospora caninum* infection in a dog. J Am Vet Med Assoc 197:87, 1990
287. Calvert CA. Valvular bacterial endocarditis in the dog. J Am Vet Med Assoc 180:1080, 1982
288. Calvert CA, Greene CE. Bacteremia in dogs: diagnosis, treatment, and progress. Compend Cont Educ Pract Vet 8:179, 1986
289. Calvert CA, Greene CE, Hardie EM. Cardiovascular infections in dogs: epizootiology, clinical manifestations, and prognosis. J Am Vet Med Assoc 187:612, 1985
290. Greene RT, Levine JF, Breitschwerdt EB, et al. Clinical and serological evaluations of induced *Borrelia burgdorferi* infection in dogs. Am J Vet Res 49:752, 1988
291. Magnarelli LA, Anderson JF, Kaufmann AF, et al. Borreliosis in dogs from southern Connecticut. J Am Vet Med Assoc 186:955, 1985
292. Magnarelli LA, Anderson JF, Schreier AB, et al. Clinical and serologic studies of canine borreliosis. J Am Vet Med Assoc 191:1089, 1987
293. Edwards NJ, Rebhun WC. Generalized cryptococcosis: a case report. J Am Anim Hosp Assoc 15:439, 1979
294. Maddy KT. Disseminated coccidioidomycosis of the dog. J Am Vet Med Assoc 132:483, 1958
295. Reed RE. Diagnosis of disseminated canine coccidioidomycosis. J Am Vet Med Assoc 128:196, 1956
296. Barsanti JA, Jeffery KL. Coccidioidomycosis. *In* Greene CE (ed): Infectious Diseases of the Dog and Cat. Philadelphia, WB Saunders, 1990, p 696
297. Wood GL, Hirsh DC, Selcer RR, et al. Disseminated aspergillosis in a dog. J Am Vet Med Assoc 172:704, 1978
298. Mullaney TP, Levin S, Indrieri RJ. Disseminated aspergillosis in a dog. J Am Vet Med Assoc 182:516, 1983
299. Littman MP, Goldschmidt MH. Systemic paecilomycosis in a dog. J Am Vet Med Assoc 191:445, 1987
300. Patnaik AK, Liu SK, Wilkins RJ, et al. Paecilomycosis in a dog. J Am Vet Med Assoc 161:806, 1972

28

Feline Cardiomyopathies

PHILIP R. FOX

DEFINITIONS AND CLASSIFICATION

Cardiomyopathy (*cardio* heart, *myo* muscle) describes a heterogeneous class of disorders whose dominant feature represents structural abnormality and functional impairment of the heart muscle.[1–3] As such, these myocardial diseases exclude conditions resulting from valvular, hypertensive, vascular, pericardial, pulmonary, or congenital derangements. Advancements in echocardiographic technology, coupled with its widespread application, have resulted in increased clinical awareness of these conditions and improved diagnostic reliability.[4–7] Cardiomyopathies constitute the major category of cardiovascular diseases encountered in clinical practice.

A variety of schemes have been proposed to define the cardiomyopathies.[1–3, 8] The term *idiopathic* (primary) *cardiomyopathy* has been applied classically to describe the myocardium as the sole source of heart disease when etiology cannot be identified, whereas *secondary cardiomyopathy* has denoted heart muscle disease resulting from an identifiable systemic, metabolic, or nutritional disorder. In 1996, the World Health Organization/International Society and Federation of Cardiology Task Force expanded the original classification to include four types of idiopathic heart muscle disease: hypertrophic, dilated, restrictive, and arrhythmogenic right ventricular cardiomyopathy.[3] In addition, the term *specific cardiomyopathies* is applied to describe heart muscle diseases associated with specific cardiac or systemic disorders, such as hypertensive cardiomyopathy, ischemic cardiomyopathy, metabolic cardiomyopathy, and others.

Accordingly, classification in cats is facilitated by clinical, pathologic, or physiologic information corresponding to (1) morphologic phenotype (e.g., hypertrophic or dilated cardiomyopathy); (2) etiology (e.g., taurine deficiency myocardial failure; thyrotoxic heart disease); (3) myocardial function (e.g., systolic or diastolic dysfunction); (4) pathology (e.g., infiltrative cardiomyopathy); and (5) pathophysiology (e.g., restrictive cardiomyopathy). Unfortunately, any scheme is self-limiting, and many cases have overlapping features or do not fit readily into a particular category. This has given rise to the increasingly acknowledged designation of *unclassified cardiomyopathies*.[3, 8]

Despite these and other difficulties in diagnosis and classification, there remains the practical problem of treating heart failure and clinical abnormalities associated with myocardial disease. As long as one recognizes that categories have no sharply defined boundaries, however, categories of cardiomyopathy continue to provide clinical utility. Important causes of cardiomyopathies are listed in Table 28–1.

TABLE 28–1
Causes of Feline Myocardial Disease

Idiopathic
- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy
- Dilated cardiomyopathy
- Arrhythmogenic right ventricular cardiomyopathy

Secondary (Including Specific Cardiomyopathies)

Inflammatory
- Viral (panleukopenia?)
- Bacterial
- Protozoal
- Fungal
- Algal
- Parasitic

Metabolic
- Nutritional
  - Taurine deficiency
  - Obesity
- Endocrine
  - Thyrotoxicosis
  - Acromegaly
  - Diabetes mellitus
  - Uremia
  - Cushing's syndrome
- Toxic
  - Anthracyclines (Adriamycin)

Infiltrative
- Neoplastic
- Glycogen storage disorders
- Mucopolysaccharidosis

Fibroplastic
- Endomyocardial fibrosis
- Endocardial fibroelastosis

Genetic
- Hypertrophic cardiomyopathy

Neuromuscular
- Facioscapulohumeral muscular dystrophy
- Duchenne muscular dystrophy

Physical Agents
- Heat stroke

Unclassified Cardiomyopathies
- Idiopathic unclassified cardiomyopathy
- Persistent atrial standstill

Miscellaneous
- Ischemia
- Excessive left ventricular moderator bands

INCIDENCE OF CARDIOMYOPATHY

There are always limitations in estimating disease incidence. Prevalence information is influenced by diagnostic criteria, survey methods, clinical and morphologic heterogeneity, and uncertainties in classification.[4–11] Because most data have originated from a few major referral institutions, the highly selective nature of patient referral patterns affects how these diseases are perceived. This can result in overestimation of disease prevalence in the general population.[10] For example, an Animal Medical Center pathology survey of 4933 consecutive feline autopsies conducted between 1962 and 1976 reported an 8.5 percent incidence of primary myocardial disease, with a male predominance (60 percent male, 40 percent female). By comparison, congenital heart anomalies were detected in 1.9 percent of this population.[9] Although extensive, this study preceded clinical appreciation of hyperthyroidism (the most common cause of secondary feline cardiomyopathy, with a current incidence of 1 percent to 2 percent at The Animal Medical Center), systemic hypertension, and echocardiography. In contrast, a restrictive view of prevalence may result from epidemiologic studies that rely solely on morphologic data, such as are generated by echocardiography or necropsy. This has been illustrated by human genetic screening surveys that utilize molecular markers to detect affected genotypes, even in the absence of structural abnormalities.[11]

In spite of these limitations, however, necropsy and echocardiographic data clearly indicate that cardiomyopathies comprise the most important category of feline cardiovascular diseases and that congenital heart diseases are relatively rare. More detailed demographic information is contained in sections discussing individual myocardial disorders (Fig. 28–1).

IDIOPATHIC (PRIMARY) CARDIOMYOPATHIES

HEART FAILURE DUE TO DIASTOLIC DYSFUNCTION: HYPERTROPHIC AND RESTRICTIVE CARDIOMYOPATHY

OVERVIEW OF DIASTOLIC FUNCTION

Abnormalities of left ventricular (LV) diastolic function may produce significant hemodynamic abnormalities. These can cause or contribute to heart failure even when systolic function is normal.[12–17] Unfortunately, diastolic function represents a complex sequence of many congruent events whose interrelationships are conceptually difficult and remain poorly defined. Moreover, diastolic dysfunction is difficult to diagnose or differentiate from systolic dysfunction based on history, physical examination, electrocardiography (ECG), and radiography.[12, 15–20]

PHYSIOLOGY OF DIASTOLIC FUNCTION

Diastolic function encompasses several distinct and different hemodynamic phases. Classically, the cardiac cycle is divided into systole and four diastolic phases (isovolumetric relaxation; rapid filling; slow filling, or diastasis; and atrial contraction, or late-filling phase)

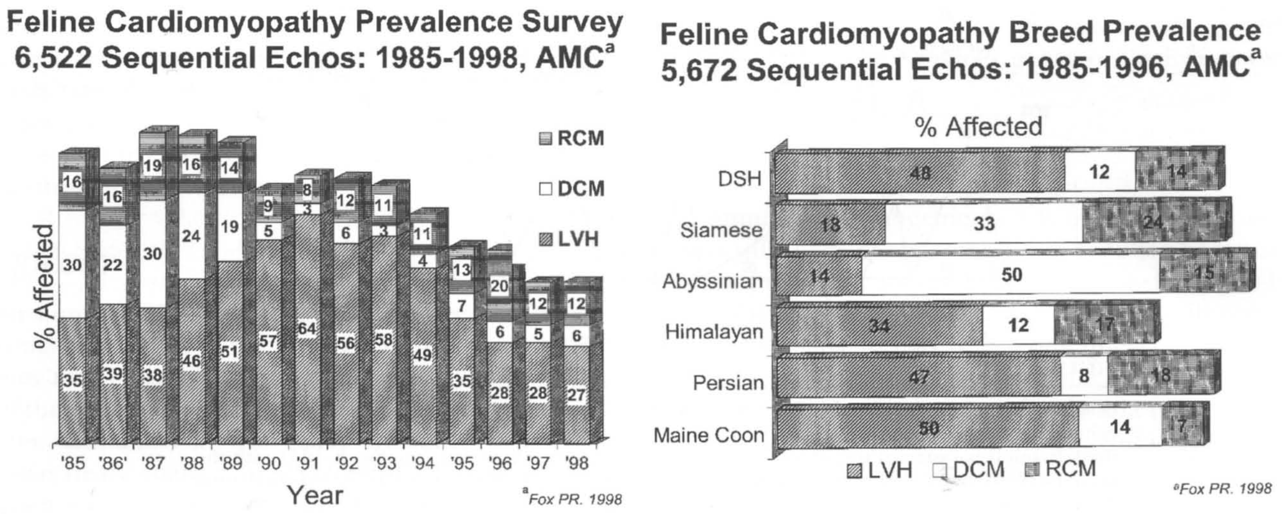


FIGURE 28–1

Prevalence of feline cardiomyopathy based upon consecutive echocardiographic examinations at The Animal Medical Center. Cats were presented for cardiovascular evaluation based upon a clinical suspicion of heart disease. Cases originated from New York City, Long Island, southern New York State, northern New Jersey, and southern Connecticut. The incidence data do not add up to 100 percent because only those cats that had myocardial disease compatible with a diagnosis of dilated cardiomyopathy *(DCM)*, restrictive cardiomyopathy *(RCM)*, or pathologic left ventricular hypertrophy *(LVH)* are listed. (A) Prevalence of DCM, RCM, and LVH diagnosed between 1985–1998. Known cases of hyperthyroidism or systemic hypertension were not included, and the LVH category represents predominantly idiopathic hypertrophic cardiomyopathy. Data for 1998 are limited to the first trimester. (B) The prevalence of feline breeds diagnosed with RCM, DCM, and LVH between 1985–1996 are compared. (Fox PR. Unpublished data, 1998.)

(see Fig. 3–14).[12, 17] A simpler and perhaps more clinically useful approach considers the cardiac cycle in terms of three segments: systolic contraction (encompassing isovolumetric contraction and the first half of ejection), relaxation (consisting of a large portion of the second half of ejection, isovolumetric relaxation, and rapid filling), and filling (beginning from mitral valve opening and ending in its closure, during which the ventricle fills with blood from the left atrium).[15] Major determinants of left ventricular filling are (1) *ventricular relaxation* (i.e., the rate and duration of the decrease in LV pressure after systolic contraction), an energy-dependent process during which contractile elements are deactivated and the myofibrils return to their precontractile length; and (2) effective chamber *compliance* (i.e., the rate of change of volume per rate of change in pressure).

EFFECTS OF DISEASE STATES ON DIASTOLIC FUNCTION

Disease states may alter diastolic function through many pathways. Three important mechanisms controlling relaxation are (1) inactivation (i.e., disengagement of actin-myosin cross bridges (influenced by intracellular calcium concentration, metabolic and neurohumeral [sympathomimetic] control, and adenosine triphosphate (ATP) concentrations); (2) LV loading forces; and (3) heterogeneity of relaxation (ischemia, infarction, or arrhythmias can cause different ventricular segments to relax asynchronously, thereby reducing chamber relaxation rate).[18–20] Chamber compliance can be reduced by increased myocardial stiffness, pericardial constraint, or increased chamber volume. These alterations in diastolic function will increase LV filling pressure and mean left atrial (LA) pressure and can result in pulmonary edema. Clinically, relaxation abnormalities may occur with myocardial ischemia, hypoxia, hypertrophy, and other factors. Ventricular hypertrophy and abnormal ventricular chamber cavity, endomyocardial fibrosis, and myofibril architectural disarray may result from a variety of primary or secondary myocardial disorders[1, 4–7, 9, 13, 21–26a]

ASSESSMENT OF DIASTOLIC FUNCTION

Diastolic function may be measured by a number of techniques. Invasive methods such as peak negative change in left ventricular pressure over time (dP/dt) and the time constant of relaxation (*tau*) are accepted indexes of the rate of relaxation.[12] However, these techniques are not performed in the clinical setting. A noninvasive and practical technique to assess diastolic function is Doppler echocardiography. When a pulsed-wave Doppler echo-sampling gate is placed at the tips of the mitral valve leaflets, peak velocity measurements indicate the relative instantaneous pressure change between the LV and LA. Resultant transmitral flow veloc-

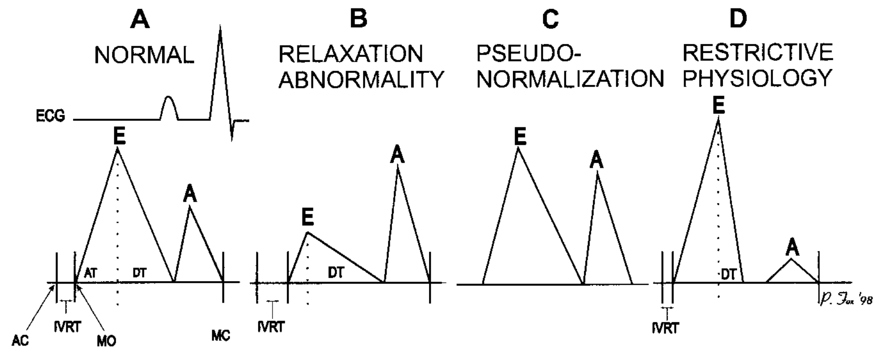


FIGURE 28–2

Diagram depicting transmitral inflow velocity patterns obtained by pulse wave Doppler echocardiography in normal states and with diastolic dysfunction. Optimal recordings are made at the left apical parasternal transducer location, four-chamber inflow view (see Fig. 8–10A) with the pulsed-wave Doppler echo sample volume gate positioned at the mitral valve leaflet tips in diastole. Alterations in velocity profiles occur in myopathic conditions that share similar diastolic properties, and there is overlap in Doppler patterns between disease states. Documentation of these classic filling patterns in cats is often frustrated by rapid feline heart rates and attendant summation of E and A waves. (A) *Normal*–In healthy cats with normal left-sided pressures, a high-velocity early diastolic filling wave (E wave) is followed by a smaller (lower velocity) late diastolic wave caused by atrial contraction (A wave). The isovolumic relaxation time *(IVRT)* is an index of LV relaxation. It represents the time from aortic valve closure *(AC)* (approximated from the Doppler spectral trace as the time from cessation of aortic blood flow), to mitral valve opening *(MO)*. *MC*, mitral valve closure. (B) *Relaxation abnormality*–Impaired LV relaxation may be indicated by a low early peak velocity (E wave) and very high atrial velocity (A wave). The IVRT is prolonged, the acceleration time *(AT)* is reduced, and the deceleration time *(DT)* is prolonged. Left ventricular diastolic pressures may be increased. (C) *Pseudonormal*–"Pseudonormalization" describes an apparently normal pattern that is actually a transition between impaired relaxation and restrictive physiology. (D) *Restrictive physiology*–Typical features include a high early velocity (E wave) and a very low atrial velocity (A wave). Both the IVRT and DT are shortened. This pattern may accompany markedly elevated LV filling pressures.

ity curves can be interpreted as a representation of the overall diastolic cardiac filling characteristics (Fig. 28–2) and have been useful in diagnosis, prognosis, and treatment of diastolic function in human patients.[12, 15, 27–30]

Abnormal LV relaxation is a common manifestation of hypertrophic cardiomyopathy. The most characteristic Doppler echo feature of a *relaxation abnormality* is low E velocity, with prolonged deceleration, and high A velocity. The "normalization" of a previously abnormal filling pattern, called *pseudonormalization,* may represent deterioration of LV diastolic function. A *restrictive filling pattern* is present in some patients with restrictive cardiomyopathy and appears as a high E velocity, with rapid deceleration and small A velocity.[8a, 14, 15, 28–30] Similar patterns are present in some cats with hypertrophic and restrictive cardiomyopathy (Fig. 28–2). In normal cats, the E velocity is generally slightly larger than the A velocity (see Table 8–4). Unfortunately, mitral flow velocities may vary with loading conditions, age, and heart rate.[12, 31, 32] Also, E and A wave velocities may summate owing to rapid feline heart rates, making interpretation difficult.

HYPERTROPHIC CARDIOMYOPATHY

DEFINITIONS AND NOMENCLATURE

Hypertrophic cardiomyopathy (HCM) is characterized by a hypertrophied, nondilated left ventricle in the absence of other cardiac disease (e.g., aortic stenosis or arterial hypertension) or systemic or metabolic abnormalities capable of producing the magnitude of hypertrophy evident. The hallmark histopathologic feature is myocyte disarray.[3, 9, 21, 24–26a] A distinctive clinical feature in some affected cats is a dynamic LV outflow tract obstruction and related subaortic pressure gradient (obstructive form of HCM).[25]

PREVALENCE AND DEMOGRAPHICS

Liu reported a 5.2 percent incidence of HCM based upon 4933 consecutive feline necropsies at The Animal Medical Center between 1962 and 1976.[9] A 1.6 percent prevalence of HCM was reported from a retrospective study of cats treated at the veterinary teaching hospital of North Carolina State University from 1985 to 1989.[33] Between 1985 and 1997, left ventricular hypertrophy (predominantly idiopathic HCM) was diagnosed in 26 percent to 64 percent of the cats examined for suspected heart disease by the Cardiology Service of The Animal Medical Center (see Fig. 28–1*A*). The reported ages of cats diagnosed with HCM range from 3 months to 17 years,[4–7, 25, 26, 33–39] with a mean age of 4.8[38] to 7 years.[25] Domestic shorthair cats are most frequently reported, followed by the domestic longhair. In certain breeds, HCM may be heritable. The strongest evidence for this is in Maine coon cats,[39, 40] American short-

hairs,[41] and Persians.[9, 24, 38] In contrast, HCM appears uncommonly in the Siamese, Burmese, and Abyssinian breeds (see Fig. 28–1*B*). A male predominance (up to 87 percent) has been widely reported.[4–9, 25, 26, 33, 35, 37] The nonobstructive form of HCM is more common than the obstructive form.

ETIOLOGY

In humans, HCM is a familial disorder with an autosomal dominant pattern of transmission caused by genes that encode cardiac sarcomere protein. About half the patients have mutations in one of six identified genes. Mutations in the genes encoding cardiac β-myosin heavy chain, cardiac troponin T, and α-tropomyosin account for up to 70 percent of human familial HCM; mutations of cardiac myosin-binding protein C, ventricular myosin essential light chain, and ventricular myosin regulatory light chain genes have been reported, and a seventh gene, cardiac troponin 1, is suspected.[42–48] The β-myosin heavy chain gene located on chromosome 14 is most commonly responsible for human HCM, and mutations in this gene disrupt sarcomere assembly and cause sarcomere disarray, the hallmark of HCM.[46] HCM is genetically heterogeneous, meaning that mutations in different genes can produce the same clinical and phenotypical disease (i.e., pathologic hypertrophy).[47] Many missense mutations of these genes have been identified. Phenotype-genotype associations could be important for clinical management and breeding. For example, disease onset is delayed and prognosis is better with human HCM caused by mutations of cardiac myosin protein C gene compared with β-myosin heavy chain gene.[48]

Evidence for genetic transmission of feline HCM is mounting. A heritable form of HCM has been identified in a highly interrelated colony of Maine coon cats, compatible with autosomal dominance with 100 percent penetrance.[39, 40] Familial transmission suggestive of an autosomal dominant pattern has also been reported in related American shorthair cats with systolic anterior motion of the mitral valve and/or HCM,[41] and in an inbred colony of Persian cats with left ventricular hypertrophy.[38] Nonfamilial forms of human HCM occur as well in which neither parent of the affected individual has the disorder. De novo gene mutations, especially cardiac β-myosin heavy chain gene, can be causative.[40] Potentially, this may take place in cats as well.

Although HCM is a genetic disease involving mutations of genes that encode proteins of the sarcomere, feline HCM and human HCM contain many gross and histopathologic structural abnormalities involving connective tissue elements. These include mitral valve anomalies, abnormal intramural coronary arteries, and collagen matrix derangements.[21, 24–26] This may suggest that phenotypic expression of HCM is influenced by factors other than the sarcomeric genetic mutation, including modifier genes or environmental triggers.[43, 50, 51]

PATHOPHYSIOLOGY

A number of derangements may occur in HCM associated with diastole. In some cases, systolic abnormalities are present in addition to diastolic dysfunction. In any particular patient, one or more of these pathophysiologic mechanisms may be of consequence, including (1) diastolic dysfunction, (2) dynamic ventricular outflow obstruction, (3) myocardial ischemia (4) ventricular and supraventricular arrhythmias, and occasionally, (5) end-stage myocardial failure.

Diastole

DIASTOLIC DYSFUNCTION. In humans with HCM, abnormal diastolic function is independent of the presence or absence of symptoms or morphology (i.e., obstructive or nonobstructive HCM).[30, 53–55] In cats, LV diastolic dysfunction has also been documented with HCM and associated congestive heart failure.[13, 25, 56, 57]

Doppler echo filling dynamics appear to be nonuniform within the LV. In human HCM patients' filling dynamics are influenced (reduced) by the extent of ventricular septal hypertrophy[58] and result from nonuniform ventricular relaxation[51] and stiffness.[52] These abnormalities may have clinical importance. For example, as a consequence of delayed LV relaxation and abnormal distensibility (stiffness), left-sided heart filling pressures increase.[59, 60] The LA dilates in response to increased end-diastolic pressures, and pulmonary venous pressures may eventually become elevated. Pulmonary congestion may result from this and other associated neurohormonal changes. Factors that can contribute to abnormal ventricular filling and stiffness include abnormal cytosolic calcium kinetics,[61] abnormal loading conditions,[20] fibrosis and myofiber disarray,[25, 26, 62] hypoxia, or ischemia.[63, 64]

MYOCARDIAL ISCHEMIA. Intrinsic diastolic function becomes abnormal when myocardial ischemia occurs.[26a, 64] Cats with HCM have coronary remodeling (arteriosclerosis or "small vessel disease") similar to that of humans with HCM.[26, 26a, 65, 66] These pathologic changes are associated with abnormally thickened arteriolar walls that reduce the lumen diameters.[24–26a, 67] The severity of coronary flow reserve is related to the degree of coronary microcirculation remodeling and myocardial hypertrophy.[68] In addition to qualitative changes in coronary microcirculation, quantitative changes in subendocardial coronary arteriolar density have been reported, with corresponding impairment of coronary vasodilator capacity in human HCM patients.[68a] These changes may predispose to myocardial

ischemia and could explain alterations of myocardial metabolism that have been identified, even in asymptomatic HCM patients.[68b] Other causes of myocardial ischemia include elevated LV filling pressures[1, 69] and prolonged diastolic relaxation,[13] resulting in increased myocardial wall tension; and LV outflow tract gradients and tachyarrhythmias[25] that can increase myocardial oxygen demand.[70–72]

VENTRICULAR AND SUPRAVENTRICULAR TACHYARRHYTHMIAS. Elevated heart rates diminish systolic and diastolic function;[72] reduce diastolic filling, which can increase outflow gradients; and reduce forward cardiac output.[12, 14] Excessive myocardial oxygen utilization and ischemia may result,[71] increasing myocardial stiffness and reducing ventricular filling. Fibrosis contributes importantly to the arrhythmogenic myocardial architecture by enhancing re-entrant excitation (chapter 16), particularly in ischemic heart disease.[72a]

Systole

DYNAMIC LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION. Hypertrophic obstructive cardiomyopathy (HOCM), an entity of HCM, is associated with several characteristic abnormalities:[25, 26a, 73–88] (1) narrowing of the LV outflow tract, (2) systolic anterior motion (SAM) of the mitral valve (Fig. 28–3), and (3) production of an LV outflow tract pressure gradient (Fig. 28–4). The LV outflow tract is formed by the hypertrophied interventricular septum anteriorly and the anterior mitral valve leaflet posteriorly. Dynamic LV outflow tract obstruction is commonly associated with systolic apposition of the mitral apparatus with the hypertrophied interventricular septum[25, 73, 74, 76, 77, 79, 80, 84–86] and has stimulated great controversy. A number of mechanisms have been proposed, including narrowing of the subaortic outlet; longer anterior and posterior mitral leaflets and anteriorly displaced papillary muscles that poorly support leaflet tissue; increased left ventricular outflow velocities; a Venturi effect that sucks the mitral leaflet toward the septum; and a high-velocity turbulent flow in the ascending aorta as a consequence of systolic anterior motion of the mitral valve.

In one echo/Doppler study of feline HCM, systolic anterior motion and dynamic left ventricular outflow obstruction were recorded in 42 percent of the cats. The magnitude of LV outflow tract obstruction varied from trivial to severe (gradients estimated by Doppler echo, 26 to 110 mmHg).[25] These LV outflow tract gradients may be present at rest or can be provoked and accentuated with stress and excitement.

Dynamic outflow tract obstruction and associated pressure gradients are potentially deleterious for several reasons.[1] They can result in increased systolic intraventricular pressure (and thereby increase myocardial wall stress); exacerbate subendocardial ischemia; increase myocardial oxygen demand; and stimulate ventricular hypertrophy. The dynamics of intraventricular and LV outflow tract gradients, systolic anterior motion of the mitral valve leaflets, and cardiac responses are labile. Stimuli that may promote or exacerbate LV outflow gradients include (1) reduced LV volume (preload), (2) decreased afterload, and (3) increased contractility.[1, 14, 74, 75, 86–89]

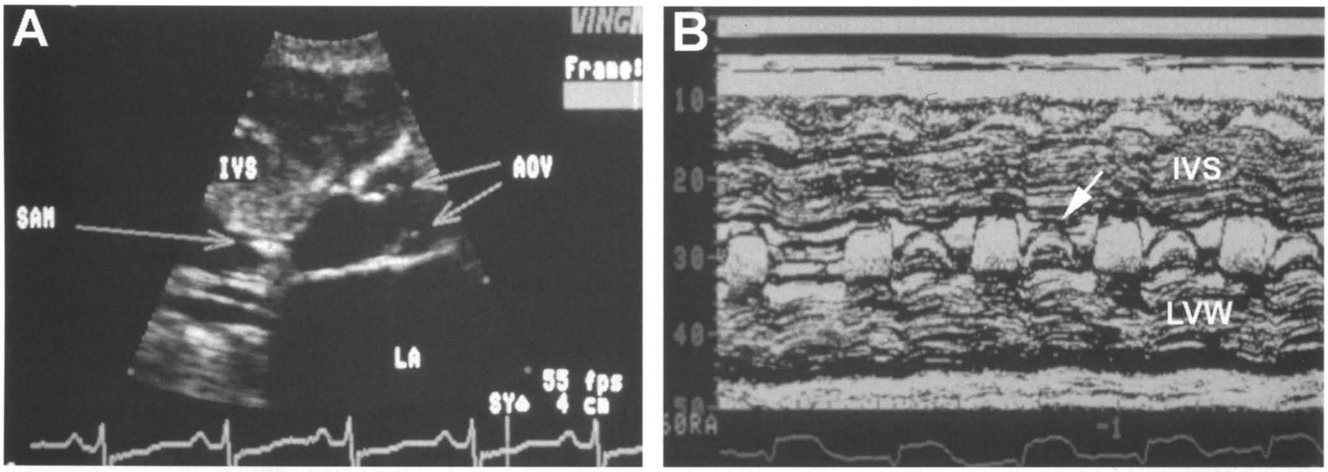


FIGURE 28–3

Dynamic left ventricular outflow obstruction in feline hypertrophic cardiomyopathy defined with echocardiography. (A) Two-dimensional recording (right parasternal long axis view). During systole, systolic anterior motion *(SAM)* with mitral valve-septal contact is present *(arrow)*. Notice the aortic valve leaflets *(AOV)*, which are open during ejection. The left atrium *(LA)* is enlarged. *IVS*, interventricular septum. (From Fox PR, Liu SK, Maron BJ: Echocardiographic assessment of spontaneously occurring feline hypertrophic cardiomyopathy: An animal model of human disease. Circulation 92:2645, 1992, with permission.) (B) M-mode tracing showing marked SAM and prolonged contact between anterior mitral leaflet and thickened IVS, producing an outflow gradient of 90 mmHg. *LVW*, left ventricular posterior wall.

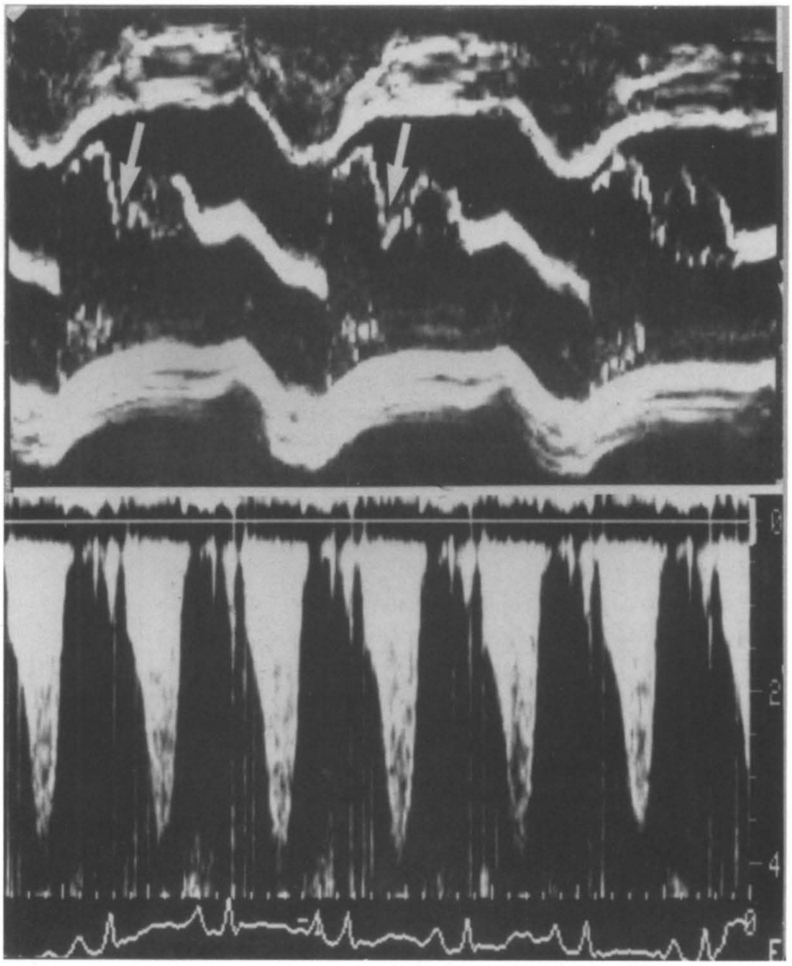


FIGURE 28–4

Evidence of dynamic left ventricular outflow obstruction in a cat with hypertrophic cardiomyopathy. *Top:* M-mode echocardiographic tracing showing partial premature closure of aortic valve leaflets *(arrows)* during systole. This corresponds to obstruction of left ventricular outflow. *Bottom:* Continuous-wave Doppler waveform shows peak velocity occurring in mid-systole (3.8 m/sec; estimated outflow gradient, 55 mmHg). (From Fox PR, Liu SK, Maron BJ: Echocardiographic assessment of spontaneously occurring feline hypertrophic cardiomyopathy: An animal model of human disease. Circulation 92:2645, 1992, with permission.)

MID LEFT VENTRICULAR GRADIENT. In addition to or instead of LV outflow tract gradient, some HCM cats have a mid-LV gradient as detected by Doppler echocardiography. A similar finding has been recorded in some humans with HCM.[30] Hypertrophied papillary muscles and hyperdynamic contractility have been postulated as causes.

MITRAL REGURGITATION. Dynamic mitral regurgitation (MR) frequently accompanies HCM with obstruction in humans[90, 90a] and cats.[25] When SAM is evident, MR results from systolic, anterior malposition of the mitral valve and increased tension on leaflets caused by papillary muscle displacement.[73] The resultant MR jet is usually directed posterolaterally (Fig. 28–5). The related cardiac murmur in cats generally becomes louder as the pressure gradient (and degree of SAM) increases. Negative inotropes can eliminate midventricular septal contact and LV outflow obstruction in people[74] and cats.[91] When the gradient and SAM are markedly reduced or eliminated by these therapies (particularly β-blocking drugs), both the degree of MR and the loudness of the murmur decrease in many cats.

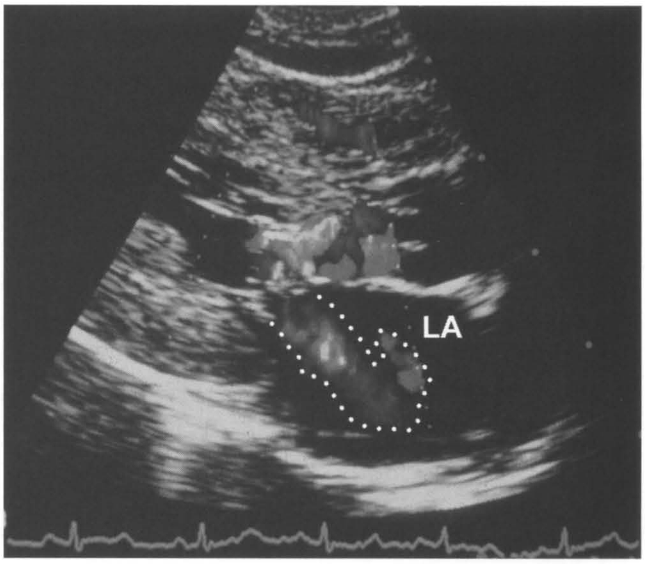


FIGURE 28–5

Two-dimensional echocardiogram (right parasternal long axis view) with color-flow imaging (shown in black and white) of a cat with HCM. There is dynamic LV outflow obstruction (estimated outflow gradient, 60 mmHg), which is associated with systolic anterior motion of the mitral valve. Mild mitral regurgitation (outlined) results from disruption of the mitral apparatus. The left atrium *(LA)* is moderately enlarged.

RIGHT VENTRICULAR OUTFLOW TRACT OBSTRUCTION AND PRESSURE GRADIENTS. Systolic abnormalities are not limited to the left ventricle. Right ventricular (RV) outflow tract gradients have been recorded from cats with HCM.[92] In humans, RV outflow tract pressure gradients also occur, and a morphologic basis has been attributed to muscular hypertrophy of the crista supraventricularis, moderator band, or trabeculae.[93] In cats, the etiology is undetermined, and most gradients are relatively mild (< 25 mmHg).

REGIONAL LEFT VENTRICULAR SYSTOLIC DYSFUNCTION. Regional heterogeneity of left ventricular systolic dysfunction has also been demonstrated. Whereas left ventricular ejection performance may be normal, segmental myocardial function (i.e., fractional thickening and circumferential shortening) is reduced in areas of thickened myocardium. Increased local wall thickness is related to worsening local wall function and may reflect regional variation in myocardial fiber disarray and fibrosis.[94, 95]

END-STAGE MYOCARDIAL FAILURE. The clinical course of cats with HCM is commonly characterized by acute, life-threatening congestive heart failure (typically pulmonary edema), often with concomitant arterial thromboembolism. Many cases remain asymptomatic. Occasionally, HCM progresses to a stage of chamber dilatation and systolic dysfunction. In humans, this structural and functional evolution is due to severe myocyte death and massive replacement fibrosis, probably associated with impaired coronary vasodilator reserve and myocardial ischemia produced by an abnormal coronary microcirculation.[95a] Similar coronary and myocardial lesions are observed in cats with suspected end-stage HCM (Fox PR, Liu SK, unpublished data, 1998). This phase that resembles dilated cardiomyopathy is usually associated with refractory heart failure and poor prognosis and occurs in approximately 1 percent to 5 percent of human HCM patients per year.[96, 97] The incidence of evolution of HCM into end-stage myocardial failure in felines is uncertain. The cause of this phenomenon has not been elucidated, although impaired responses to isoproterenol infusion have been related to future deterioration of LV performance in humans with typical HCM.[98]

PATHOLOGY

The principal pathologic feature of primary (idiopathic) hypertrophic cardiomyopathy is a hypertrophied, nondilated left ventricle in the absence of causative cardiac, systemic, or metabolic disease (Figs. 28–6, 28–7).[1–3] Left ventricular hypertrophy exhibits a broad morphologic spectrum in humans[1, 26, 85, 99a] and cats.[5–7, 9, 21, 24–26, 39, 41, 99–101] Biatrial enlargement is common. Mild to moderate right ventricular hypertrophy is often present. The hallmark histopathologic lesion is left ventricular myofiber disarray (cellular disorientation in more than 5 percent of the tissue section).[9, 24–26, 99, 102, 103] Other common findings include remodeling of the coronary microcirculation associated with arteriosclerosis (small vessel disease), and matrix abnormalities characterized by myocyte necrosis and fibrous connective tissue changes (see Figs. 36–2, 36–4, and 36–5).[24–26, 65–68, 99, 102, 103] Myocardial infarction is frequently present in cats[104] and has been reported in humans—both without significant extramural (large) coronary artery disease.[105] In cats, the LV free (posterior) wall or LV apex is usually affected, although the RV free wall is occasionally involved. Necropsy may reveal left-sided congestive heart failure (CHF) (pulmonary congestion or edema) and, less commonly, right-sided CHF (pericardial, pleural, or abdominal effusions). Arterial thromboembolism (saddle thrombus) is common, often with renal infarction. Left atrial and LV thrombi are occasionally present (see also chapter 36).

CLINICAL MANIFESTATIONS

HISTORY. A broad range of clinical abnormalities have been described.[4–7, 24, 25, 33–37, 39–41, 56, 100, 101, 106] Many cats are asymptomatic. In these cases, cardiac disease often is first discovered during routine examination by the presence of a heart murmur, gallop rhythm, or arrhythmia. In other cases, peracute signs (< 24 hours) associated with pulmonary edema are heralded by severe dyspnea and orthopnea and represent the first clinical manifestation of cardiomyopathy. Occasionally, observant owners may observe tachypnea in early stages of decompensation. Anorexia and vomiting may precede respiratory signs by 1 or 2 days in some cats. Coughing is rarely observed, even in cats with fulminant pulmonary edema. Acute paresis is the second most common clinical sign and is associated with arterial thromboembolism. The back legs are most commonly affected (posterior paresis), but occasionally paresis of one front leg—generally the right front—occurs. Cats with posterior paresis are in acute pain and vocalize during the first 12 to 24 hours, whereas front leg paresis appears to be better tolerated. In the majority of cats with arterial thromboembolism, CHF is also present. Syncope occurs less commonly and may result from tachyarrhythmia or dynamic left ventricular outflow tract obstruction. Sudden death without CHF is uncommon but has been documented by the author in association with stress, sudden activity, or Valsalva maneuvers (defecation or urination).

PHYSICAL EXAMINATION. The left precordial apex beat is usually palpably normal or hyperdynamic. Auscultation may reveal a soft, systolic murmur (I to III/VI)

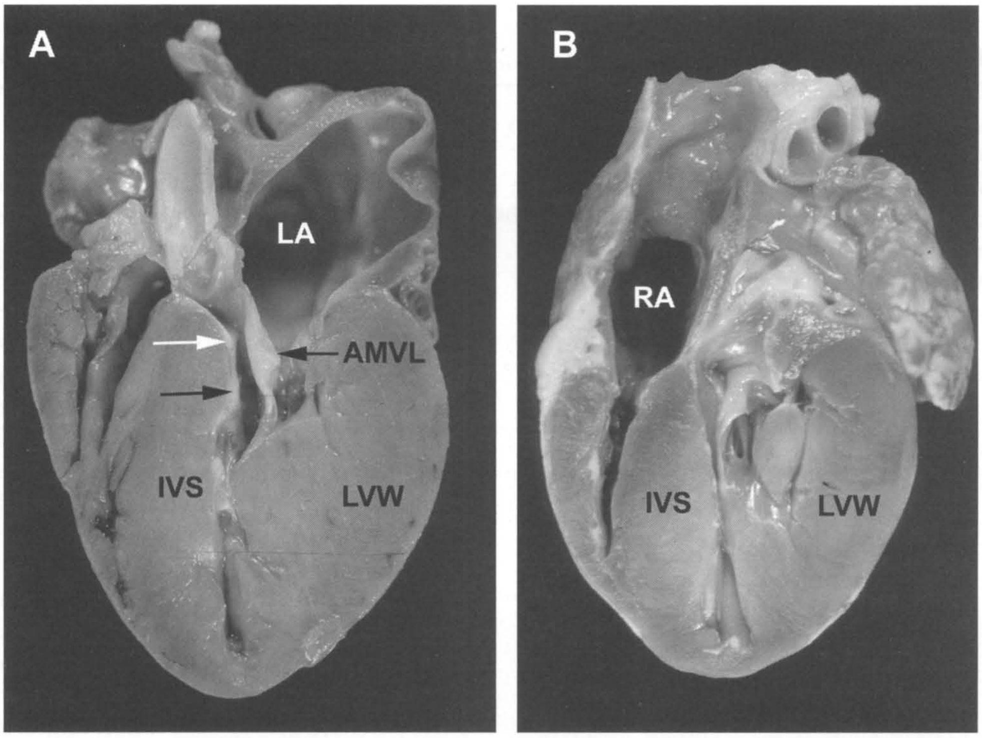


FIGURE 28–6

Gross heart specimens from two cats with hypertrophic cardiomyopathy showing patterns and distribution of left ventricular hypertrophy associated with a small left ventricular cavity. (A) Ventricular septal thickening is maximal in the basal portion, and the LV posterior wall *(LVW)* is also substantially thickened. The left atrium *(LA)* is markedly enlarged and there is right ventricular hypertrophy. The LV outflow tract has a fibrous contact plaque *(white arrow)* on the basilar interventricular septal *(IVS)* surface. This plaque is in close proximity to the anterior mitral leaflet *(AMVL)* and presumably resulted from systolic apposition of the mitral valve and ventricular septum. The septal endocardial thickening present more distally in the mid-cavity level *(black arrow)* is probably a consequence of end-systolic cavity obliteration and contact between septum and other portions of the LV wall. (B) Ventricular septal thickening is more prominent toward the LV apex than the base. The right ventricle is hypertrophied. *RA*, right atrium. (From Fox PR, Liu SK, Maron BJ. Echocardiographic assessment of spontaneously occurring feline hypertrophic cardiomyopathy: An animal model of human disease. Circulation 92:2645, 1992, with permission.)

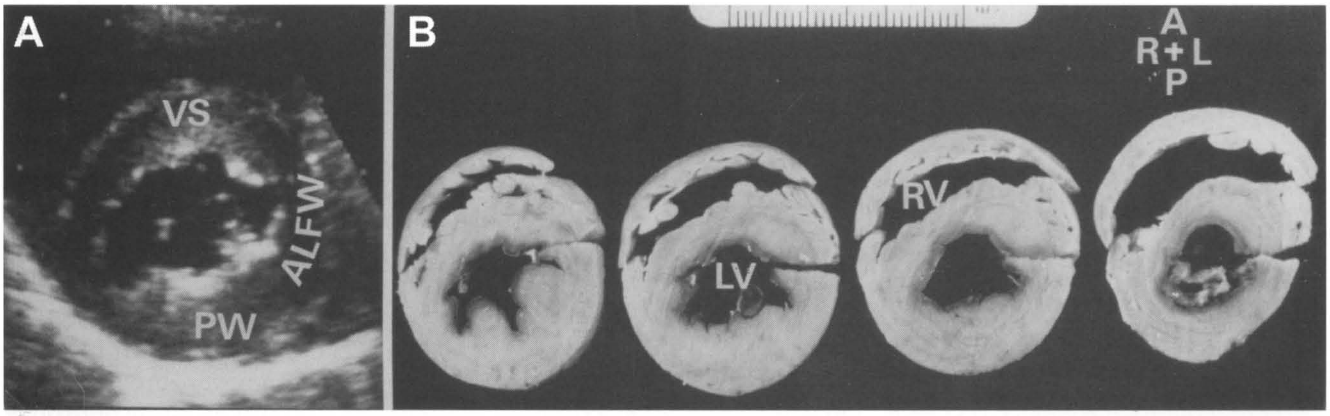


FIGURE 28–7

(A) Two-dimensional echocardiogram (right parasternal short axis view) recorded at the chordae-mitral valve level of a cat with posterior paresis from a distal aortic ("saddle") embolus. In this view pathologic hypertrophy is confined to the anterior portion of the interventricular septum *(VS)* and a region of the anterolateral free wall *(ALFW)*. A standard M-mode echo beam transecting the mid ventricular septum and left ventricular posterior wall *(PW)* would miss this focal hypertrophy. (B) Postmortem gross specimens from the same patient. The heart was sequentially sectioned from the papillary muscle level (first section at the left) to the mitral valve level (fourth section). Segmental hypertrophy is evident. *LV*, left ventricle; *RV*, right ventricle.

heard loudest over the mitral and/or tricuspid valve areas or over the sternum. A diastolic gallop rhythm is common and usually represents a fourth heart sound, S_4 (Fig. 28–8). Rales, arrhythmias, and femoral arterial pulse deficits occur commonly with CHF. Heart and lung sounds will be muffled if significant pleural or pericardial effusion is present. Paresis and absence of femoral arterial pulses accompany distal aortic thromboembolism. Abnormal jugular venous pulses may be present with severe right-sided heart failure. Ascites and cachexia are occasionally present in cases of chronic, end-stage disease.[4–7, 24, 21, 33–37, 56]

ELECTROCARDIOGRAPHY. Electrocardiographic changes are highly variable, generally nonspecific, and frequently unremarkable.[4–7, 35, 37, 56, 100, 108, 109] A left axis deviation compatible with left anterior fascicular block (see Fig. 6–24) has been reported in 11 percent (Table 28–2), 30 percent,[37] and 33 percent[100] of cats with HCM. It has been detected in 3 percent to 6 percent of cats with hyperthyroidism[107] and is infrequently recorded in other forms of myocardial disease. Other commonly recorded abnormalities include LA enlargement (P wave > 40 ms wide), LV enlargement (R_{II} > 0.8 mV tall; QRS > 40 msec wide), and ventricular and supraventricular arrhythmias. Frequently occurring arrhythmias are listed in Tables 19–1 and 28–2.

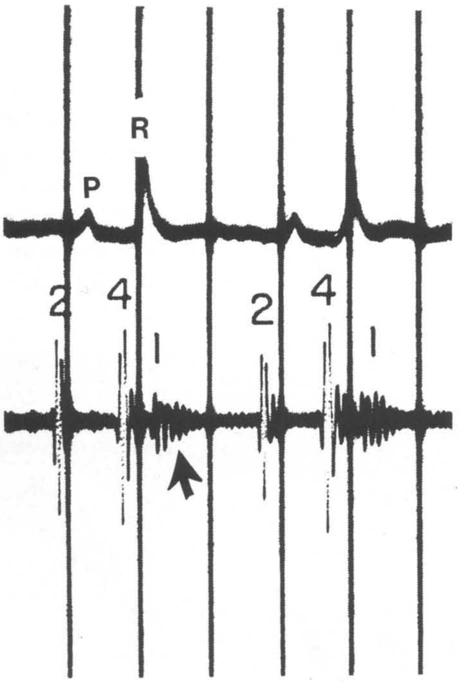


FIGURE 28–8

Phonocardiogram from a cat with hypertrophic cardiomyopathy. A simultaneous ECG is recorded above. There is a prominent atrial gallop rhythm (S_4, fourth heart sound). This can often be detected by auscultation and its timing occurs just before the first heart sound (S_1). A systolic heart murmur *(arrow)* is also present and begins after S_1. The second heart sound (S_2) is labeled and systole is defined as the interval between S_1 and S_2; *P*, P wave; *R*, R wave; paper speed, 100 mm/sec. (Modified from Tilley LP, Liu SK, Gilbertson SR, et al. Primary myocardial disease in the cat: A model for human cardiomyopathy. Am J Pathol 87:493, 1977, with permission.)

RADIOGRAPHY. Survey thoracic radiographs are necessary to determine the presence of cardiomegaly, evaluate pulmonary parenchymal and vascular changes, and assess patterns of cardiovascular alterations. The so-called "valentine-shaped" heart occurs infrequently with HCM and should not be relied upon for diagnosis. The ventrodorsal or dorsoventral view is the most sensitive position to disclose auricular enlargement (Fig. 28–9; see Figs. 7–8 and 7–9), and care should be taken to align the spine and sternum to avoid positional rotation. In symptomatic cats with pulmonary edema, the commonest radiographic changes include interstitial and/or alveolar pulmonary densities; pulmonary venous distention (congestion) with or without pulmonary arterial congestion (Figs. 28–10, 28–11; see also Figs. 7–8, 7–9, and 13–4); and occasionally, mild pleural effusion. Pulmonary edema may be diffuse, patchy, or focal in location and often involves the right caudal lung lobe (Fig. 28–11). Severe, diffuse edema is common with diastolic dysfunction (i.e., hypertrophic or restrictive cardiomyopathies) but rarely accompanies severe systolic failure (i.e., dilated cardiomyopathy). With chronic or advanced HCM, cardiomegaly may be generalized and accompanied by severe biventricular failure (e.g., pleural, pericardial, or abdominal effusion; hepatosplenomegaly; or pulmonary edema).[4–7, 35, 37, 56, 69, 100, 101, 106, 108]

ANGIOCARDIOGRAPHY. Although contrast radiography has been largely replaced by echocardiography for clinical diagnosis, nonselective angiocardiography may provide important morphologic information in some cases (Figs. 28–12, 28–13). Characteristic angiographic features of HCM include (1) LV free wall hypertrophy; (2) pronounced LV chamber reduction (which often appears slitlike in appearance); (3) extremely hypertrophied papillary muscles; (4) moderate to severe LA and sometimes RA enlargement, (5) distended pulmonary veins; (6) normal to accelerated circulatory transit time; and (7) ball thrombi in the LA or LV.[4–7, 35, 69, 110–112]

ECHOCARDIOGRAPHY. Echocardiography is required for definitive diagnosis of cardiomyopathy. It is used to (1) verify and assess the severity of LV hypertrophy and cardiac chamber dimensions, (2) detect dynamic LV outflow tract obstruction, (3) evaluate myocardial function, (4) detect intracavitary ball thrombi or prethrombotic conditions (e.g., spontaneous echo contrast formation) (Fig. 28–14), and (5) diagnose other cardiac conditions. Clinical diagnosis is based on echocardiographic identification of the most characteris-

TABLE 28–2
Frequency of Selected Arrhythmias Recorded from Cats with Cardiomyopathy

	Hypertrophic Cardiomyopathy (%) (n = 46)*	Restrictive Cardiomyopathy (%) (n = 37)†	Myocardial Failure (%) (n = 49)‡
1° AV block	0	7	37
LAFB	10	7	3
APCs	10	22	15
PAT/Atrial fib	10	2	2
VPCs	41	53	43
VT	10	7	23

*Unpublished data from cats in Fox PR, Liu SK, Maron BJ. Echocardiographic assessment of spontaneously occurring feline hypertrophic cardiomyopathy: An animal model of human disease. Circulation 92:2645, 1992.

†From Fox PR. Unpublished data, 1998.

‡From Fox PR, Petrie JP, Liu SK, et al. Clinical and pathologic features of cardiomyopathy characterized by myocardial failure in 49 cats: 1990–1995; Abstract. J Vet Intern Med 11:139, 1997. Five cats had severe taurine depletion.

LAFB, Left axis deviation compatible with left anterior fascicular block; APCs, atrial premature complexes; PAT, paroxysmal atrial tachycardia; Atrial fib, atrial fibrillation; VPCs, ventricular premature complexes; VT, ventricular tachycardia.

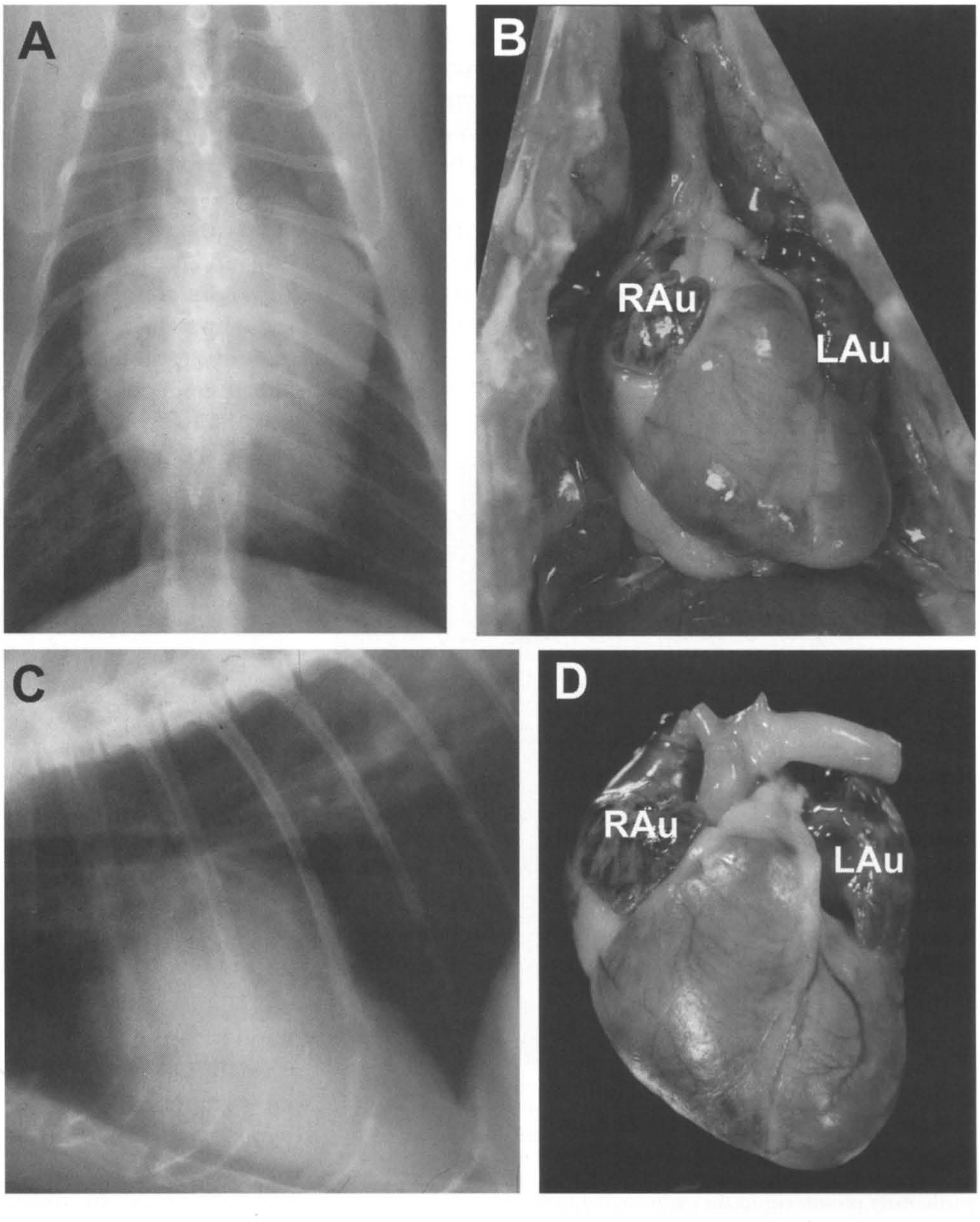


FIGURE 28–9

Correlative radiographic and necropsy anatomy of a cat that died of hypertrophic cardiomyopathy. (A) Thoracic radiograph, ventrodorsal view. (B) *In situ* heart, ventrodorsal view. Massive left auricular *(LAu)* enlargement and moderate right auricular *(RAu)* enlargement are evident. In this view the auricular appendages tend to extend out from other cardiovascular structures and thus, are more readily identified when they are enlarged. (C) Thoracic radiograph, right lateral view. (D) Explanted heart positioned to correlate with its right lateral radiographic orientation. The gross heart in this position shows marked RAu and LAu enlargement, but the auricles overlie and are radiographically superimposed over other cardiovascular structures. Thus, while cardiomegaly is evident from the lateral radiograph, the changes in the silhouette are not as striking as those in the ventrodorsal view.

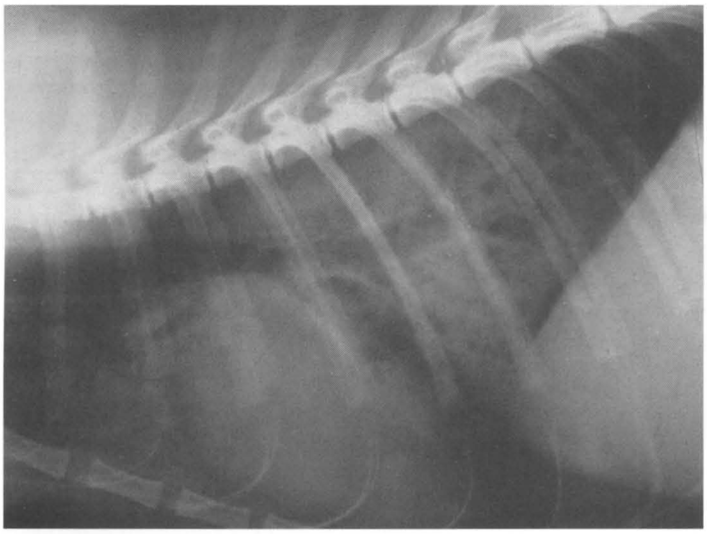


FIGURE 28–10

Right lateral thoracic radiograph from a cat with hypertrophic cardiomyopathy. There is a severe, generalized interstitial and alveolar pattern compatible with pulmonary edema.

tic morphologic expression of HCM—namely, unexplained LV wall thickening with a nondilated LV chamber, in the absence of hyperthyroidism, hypertension, or aortic stenosis. To diagnose pathologic hypertrophy, the thickness of the ventricular septum or LV posterior (free) wall measured at end-diastole must be greater than 6 mm.[25]

Hypertrophic cardiomyopathy is a heterogeneous disease. It is characterized by a broad range of phenotypic patterns of LV hypertrophy ranging from localized and relatively mild wall thickening involving any one particular wall segment, to diffuse and pronounced hypertrophy of all portions of the left ventricle (see Figs. 28–3, 28–5, 28–7, and 28–14).[25, 86, 99–101] No single pattern can be considered "classic" or characteristic of the disease. In a study assessing the distribution of LV hypertrophy in 46 cats with idiopathic HCM, four patterns of distribution of LV hypertrophy were identified.[25] Most often (31 cats), hypertrophy was diffuse and substantial, involving portions of the ventricular septum as well as the contiguous anterolateral and posterior free wall: (1) 15 of these 31 cats showed a concentric distribution of hypertrophy of all segments and (2) 16 of these 31 cats had involvement of the anterior portion of the septum as well as anterolateral and posterior free wall (but not posterior septum). Less often (the remaining 15 of the 46 cats), segmental patterns of hypertrophy (see Fig. 28–7) were seen: (3) in 13 of these 15, wall thickness was confined to only one LV segment (anterior septum in 12 and posterior free wall in 1 cat and (4) in 2 of the 15 cats, wall thickening involved noncontiguous segments of the left ventricle, ie., anterior septum or posterior free wall. When viewed from the longitudinal axis, 26 of the 46 cats showed greater wall thickening of the basal rather than apical portion of the left ventricle. Some had proximal septal thickening that protruded into the LV outflow tract. The other 20 cats had diffuse thickening involving the basal and apical left ventricle. Therefore, echocardiographic examination must incorporate multiple imaging views to integrate findings. In this regard, segmental wall thickening may be well assessed from the right, parasternal, short-axis view by evaluating a studied, continuous base-to-apical sweep, particularly when integrated with information obtained from parasternal long-axis and other views.

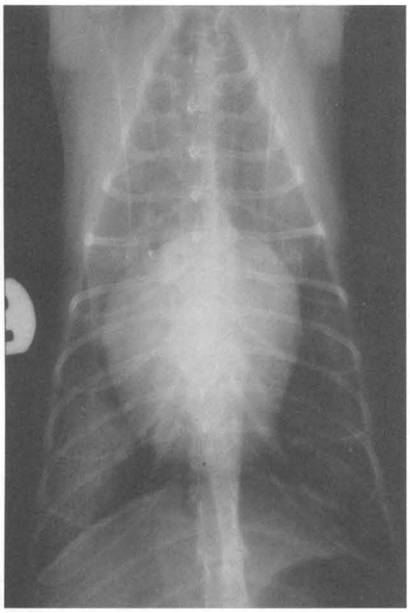


FIGURE 28–11

Ventrodorsal radiograph of a cat with hypertrophic cardiomyopathy with acute dyspnea. Interstitial and alveolar pulmonary infiltrates are present in a "patchy" distribution. This is particularly prominent in the right caudal lung lobe.

Additional echo findings include LA and often RA enlargement; decreased LV internal dimensions with hypertrophied papillary muscles; normal to elevated LV fractional shortening; mild hypertrophy of the RV wall and mild to moderate hypertrophy of the RV

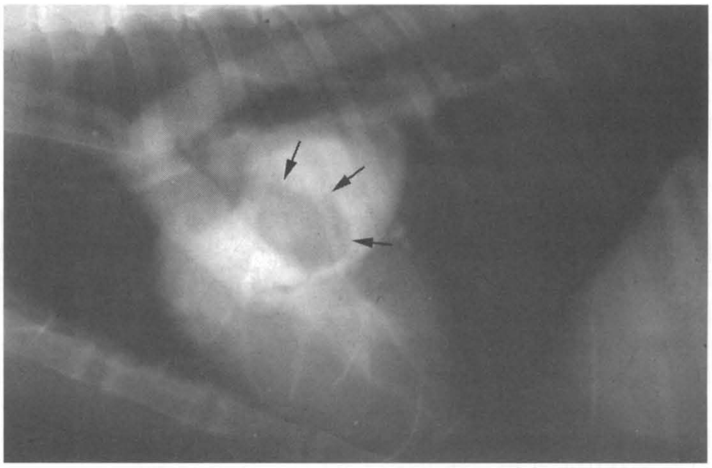


FIGURE 28–12

Nonselective angiocardiogram of a cat with hypertrophic cardiomyopathy. This exposure was taken approximately six seconds after venous injection of radiocontrast dye. A large filling defect *(arrows)* caused by a ball thrombus is present within the enlarged left atrium. The left ventricular chamber is reduced and the left ventricular posterior wall is thickened.

outflow tract; RV dilation (late in the disease course of some cases); and pericardial effusion. In cases of dynamic LV outflow tract obstruction, there is SAM of the mitral apparatus and midsystolic aortic valve closure; narrowed LV outflow tract; a fibrous plaque on the basal ventricular septum corresponding to the point of systolic anterior mitral valve contact; and thickening of the anterior mitral valve leaflet (see Fig. 28–6). Chordae tendineae may be elongated and the mitral valve leaflets enlarged.[4–6, 14, 25, 41, 73–78, 85, 100, 101]

DOPPLER ECHOCARDIOGRAPHY. A number of flow disturbances may occur.[14, 25, 30, 54, 57, 82, 90, 90a] Mitral regurgitation is common. In 46 cats with HCM, mild to moderate mitral regurgitation was detected in 96 percent, regardless of whether the obstructive or nonobstructive form was present.[25] Tricuspid regurgitation is less common. Cats with SAM usually have eccentric mitral regurgitation jets (see Fig. 28–5). These are usually oriented toward the posterolateral wall and result from systolic disruption of the mitral valve apparatus. With dynamic LV outflow tract obstruction, the maximal LV outflow tract velocity is increased. Estimated subaortic gradients using the modified Bernoulli equation (chapter 8) range from 25 to 110 mmHg.[25] These LV outflow tract Doppler waveforms display a characteristic concave and asymmetrically shaped pattern (see Fig. 28–4) because they increase relatively slowly in early systole but then rise abruptly and peak in midsystole. In addition, increased RV outflow tract gradients may occur.[92] This may be more common when LV outflow tract gradients are present.[93] Mitral inflow

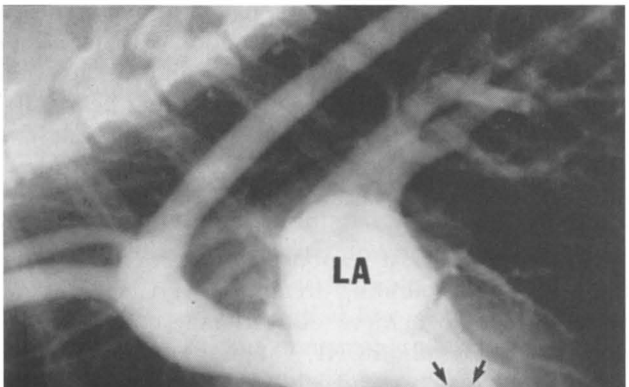


FIGURE 28–13

Nonselective angiocardiogram of a cat with hypertrophic cardiomyopathy. The left atrium (LA) is dilated, the left ventricular chamber is small, and the papillary muscles *(arrows)* and walls of the left ventricle are thick. (From Fox PR. Myocardial diseases. In Ettinger SJ (ed): Textbook of Veterinary Internal Medicine. 3rd ed. Philadelphia, WB Saunders, 1989.)

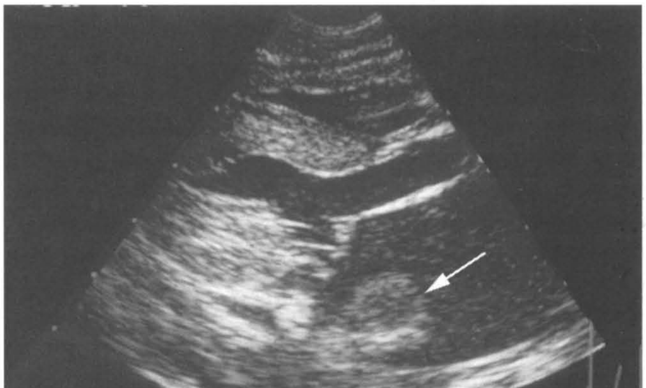


FIGURE 28–14

Two-dimensional echocardiogram (right parasternal long axis view) from a cat with dyspnea and pulmonary edema. The left atrium is severely enlarged and contains a ball thrombus attached to the posterior wall *(arrow)*. Spontaneous echo contrast ("smoke"), appearing as echogenic (white) specks, are present in the left atrium. The left ventricle is diffusely hypertrophic and scant pericardial effusion is present. Two days after this examination the cat experienced an acute distal arterial embolism.

Doppler waveforms may be normal or show a relaxation abnormality indicative of diastolic dysfunction (see Fig. 28–2).[14, 28, 30, 57] Occasionally, a mid to left ventricular gradient may be present.

CLINICAL PATHOLOGY. Effusions, when present, are obstructive transudate or modified transudate.[113] Mild prerenal azotemia may result from anorexia and vomiting, and anorectic cats usually have mild to moderate hypokalemia. These changes may be exacerbated by overzealous diuretic administration.[4–7, 113] Thromboembolism will cause elevations of serum muscle and hepatic enzymes and, occasionally, hyperkalemia.[4–8, 37, 108] Hypersomatotropism has been reported in hypertrophic cats,[114] but its significance, if any, is uncertain.

DIFFERENTIAL DIAGNOSIS

Conditions that cause LV hypertrophy must be excluded before idiopathic HCM can be diagnosed. Thus, the two most common differential diagnoses are hyperthyroidism and systemic hypertension. Rarely, valvular or subvalvular aortic stenosis is encountered. The combined presence of systemic hypertension (causing LV hypertrophy) and restrictive cardiomyopathy (causing LA enlargement) may cause morphologic changes resembling HCM. Because right-sided CHF may occur with HCM, noncardiac causes of pleural effusions must be considered. When severe pericardial effusion is present, pericardial diseases must be ruled out.

NATURAL HISTORY AND PROGNOSIS

A substantial proportion of HCM cats achieve adulthood without clinical signs or appear to have a normal life expectancy, often without the aid of major therapeutic interventions. Some cats will present with fulminant congestive failure, become compensated with drug administration, and then remain asymptomatic; some of these individuals will have recurrent bouts of CHF and ultimately die, whereas a small percentage will remain asymptomatic, even after discontinuation of medicaments. In contrast, many cats with HCM will experience CHF, thromboembolism, and death. Morbidity and mortality differ in humans with familial HCM according to the mutations involved,[48] but this has not been investigated in cats.

A disease pattern of HCM has been reported in a highly interrelated colony of Maine coon cats with familial HCM. When individuals with phenotypic LV hypertrophy ("affected cats") were mated to cats without hypertrophy ("unaffected cats"), HCM was not evident before 1 year of age; it usually became apparent during adolescence; and it usually progressed to severe disease by 2 to 4 years of age. In cats from affected to affected matings, HCM became apparent as early as 3 months of age and progressed to severe disease between 6 and 18 months of age.[39]

Unfortunately, predicting the clinical course and outcome is difficult if not impossible owing to the wide variation in complexity of disease expression, particularly since heritable characteristics are unknown. No particular clinical finding has been shown to be reliably associated with subsequent sudden death or early recrudescence of CHF. Nevertheless, some survival characteristics have begun to emerge. In a series of 46 cats with HCM in which 43 were followed for up to 49 months,[25] nonsurvivors showed a significantly greater magnitude and extent of LV hypertrophy (maximum wall thickness, 8.1 ± 1.5 mm) than survivors (7.3 ± 0.9 mm); nonsurvivors had significantly larger LA dimensions (20.1 ± 4.6 mm) compared with survivors (16.8 ± 3.4 mm). In addition, SAM was more common in survivors (16 of 18 cats [89 percent]) than nonsurvivors (10 of 21 cats [48 percent]), suggesting that the nonobstructive form of feline HCM without SAM had a more unfavorable prognosis.

In another series of 61 HCM cats for which follow-up evaluation was possible,[33] median survival time was 732 days. Longevity was not affected by age, breed, gender, or body weight, but the presence or absence of clinical signs did have an impact upon survival. For example, cats without clinical signs lived longer (median survival > 1830 days) than those with clinical signs (cats in heart failure survived a median of 92 days, and cats with arterial embolism survived a median of 61 days). At 6 months after diagnosis, all cats with embolism and 60 percent of cats with heart failure were dead. Cats with heart rates of less than 200 beats/min at initial examination survived significantly longer than those with heart rates over 200 beats/min. However, since the minimal, maximal, and mean heart rates evaluated by 24-hour continuous ECG monitoring vary considerably in normal cats and in cats with CHF,[115] the clinical relevance of presenting heart rate remains uncertain. In a series of 15 HCM cats that had CHF, a mean survival time of 1147 days was recorded, although treatments varied and no controls were included.[156]

Diminished clinical response to diuretics is a common factor confounding treatment of CHF in people.[116] Failure to achieve diuresis may contribute to greater risk of death in CHF,[117] perhaps due to inability to reduce cardiac preload, which leads to preservation of altered hemodynamics, abnormal neurohormonal activation, and increased mortality. An attenuated response to diuretics (i.e., slow or partial clearance of edema despite vigorous IV furosemide) is also associated with poor prognosis in cats.

DOES EARLY THERAPY DELAY OR REVERSE PROGRESSION OF MYOCARDIAL DISEASE?

The clinical course and outcome of feline myocardial disease are difficult to predict owing to the hetero-

geneity of each condition, the complexity of disease expression, and the wide variation in natural history. Certainly, diuretics are not indicated in asymptomatic cats who have never had CHF. Diuretics may activate the renin-angiotensin-aldosterone system, which can be potentially detrimental.[117a] There is no evidence that standard therapies can influence the powerful biologic mechanisms that dictate morphologic hypertrophy.[95a] However, it is unclear whether β-adrenergic blockers, calcium channel blockers, or angiotensin-converting enzyme (ACE) inhibitors delay disease progression, protect against sudden death, or improve prognosis in asymptomatic cases. There is currently no consensus among cardiologists regarding therapeutic approaches. However, several treatment strategies, as suggested next, may be justified based upon theoretical benefits and comparative studies in human cardiology or animal models of disease.

THERAPIES IN ASYMPTOMATIC BUT POTENTIALLY HIGH-RISK PATIENTS

No single test can reliably predict morbidity or mortality in HCM, and the complexity of the disease has created obstacles for risk identification and stratification. Nevertheless, several important features of HCM may increase risks of morbidity and mortality. Accordingly, prophylactic therapy may be warranted in these circumstances, based upon certain pathophysiologic considerations.

MYOCARDIAL INFARCTION. Myocardial infarction (MI), particularly involving the LV apex or free wall (see Figs. 36–14 and 36–15), is more prevalent in feline cardiomyopathies than once believed.[105] Clinical suspicion of MI is based upon echocardiographic evidence of regional left ventricular hypokinesis or dyskinesis, LV free wall thinning (end-diastolic measurement < 2 mm), or ECG evidence of marked (> 0.2 mV) ST segment elevation or depression. In cats and humans with HCM, myocardial infarction causes significant morbidity and may be related to intramural arteriosclerosis.[24–26, 67, 68] Myocardial ischemia is commonly associated with MI and myocardial fibrosis in humans with HCM[26, 72, 99, 103, 104] and presumably also in cats, based upon similar histopathologic lesions.[9, 21, 24–26a, 39, 67, 105] Ischemia is also strongly associated with severe and potentially lethal arrhythmias.[118]

β-ADRENERGIC BLOCKER THERAPY. Results from clinical trials evaluating myocardial infarction therapies in humans offer compelling evidence for use of β-blockers. These agents decreased mortality in patients with acute MI and cardiac arrhythmias.[119, 120] In patients with chronic MI, β-blockers reduced long-term mortality by their antiarrhythmic effects and by prevention of reinfarction, particularly when decreased contractility and ventricular arrhythmias were present.[121, 122] Even at low doses, β-blockers provided effective post-MI therapy.[123] Moreover, left ventricular diastolic function is very sensitive to increases in sympathetic tone.[124] Thus, use of sympathetic nervous system antagonists may indirectly improve ventricular compliance by reducing heart rate and myocardial ischemia. In cats with suspected ischemic myocardial injury, propranolol (Inderal, Wyeth-Ayerst; 2.5 to 5 mg q8–12h PO) or atenolol (Tenormin, Zeneca; 6.25 to 12.5 mg q12–24h PO) can be administered. Although these agents are generally safe, β-blockers may occasionally cause bradycardia, hypotension, or lethargy. Echocardiography can be useful to monitor cardiac chamber dimensions, assess LV remodeling,[126] and, in cases in which myocardial failure is related to severe MI, follow contractility since β-blockers are negative inotropes.

ANGIOTENSIN-CONVERTING ENZYME INHIBITOR THERAPY. ACE inhibitors have been advocated in human post-MI trials based upon their role in reducing cardiovascular remodeling and improving hemodynamics and survival.[127–129] There is clear evidence in people that ACE inhibitors decrease mortality in acute MI,[130] and that chronic therapy reduces ischemic events.[131] Enalapril (Enacard, Merial Ltd.; 0.5 mg/kg q24h PO) is probably the most commonly used ACE inhibitor in cats. Other agents are available, including benazepril (Lotensin, Ciba; 0.5 mg/kg q24h PO); lisinopril (Prinovil, Merial Ltd.; 0.25 to 0.5 mg/kg q24h PO); and captopril (Capoten, Bristol-Myers Squibb; 3.12 to 6.25 mg q6–8h PO). ACE inhibitors reduce blood pressure and may be contraindicated with hypotension. Overzealous concomitant diuretic therapy may cause azotemia.

CALCIUM CHANNEL BLOCKER THERAPY. Based upon extrapolation from human studies, one should exercise caution when considering these agents in cats with MI. Calcium channel blockers have not been efficacious (i.e., no reduction of subsequent cardiovascular events) with MI in people.[132, 133] Furthermore, diltiazem and other calcium-blocking agents caused harm when administered to humans with MI and left ventricular dysfunction,[134–136] possibly by activating the neuroendocrine system.[137] Accordingly, calcium antagonists are not currently recommended for routine secondary prevention after infarction.[138] Others have advocated that heart rate–lowering calcium antagonists (e.g., verapamil, diltiazem) be reserved for humans with MI but without CHF, in whom a β-blocker is contraindicated, or in conjunction with an ACE inhibitor.[129] Whether or not these data are relevant to treatment strategies for feline myocardial diseases remains to be determined.

TACHYARRHYTHMIAS. The genesis of atrial tachyarrhythmias includes electrophysiologic abnormalities as-

sociated with marked LA enlargement and concurrent derangements in atrial cell structure.[140] In addition, myocardial necrosis, fibrosis, and scar are common features of feline myocardial disease[9, 21, 22, 24–26, 67, 99, 141] and may serve as substrates for serious ventricular arrhythmia.[142] Tachycardia diminishes systolic and diastolic function,[72] reduces diastolic filling that can increase outflow gradients and reduce forward cardiac output,[12, 14] and can result in excessive myocardial oxygen utilization and ischemia.[71] Ventricular hypertrophy is associated with increased risk of sudden death in people (mechanisms include depressed resting membrane potential, increased excitability threshold, interstitial fibrosis, and abnormal intracellular calcium handling).[142a] In some cases tachycardia precipitates weakness or syncope. Beta-adrenergic blockers (propranolol, 5 to 10 mg q8–12h PO; atenolol, 6.25 to 12.5 mg q12–24h PO) antagonize the sympathetic nervous system and may therefore be useful for treating paroxysmal ventricular tachycardia or frequent multiform ventricular arrhythmias. Digoxin (0.031 mg [i.e., ¼ of a 0.125-mg tablet] per 4.5-kg cat q48h PO) or diltiazem may be administered for atrial tachyarrhythmias. However, heart rate control often requires the addition of a β-blocker, beginning with half of the initial dose, which is then titrated to effect.

MASSIVE LEFT VENTRICULAR HYPERTROPHY. Although the severity of hypertrophy is not a recognized risk factor for sudden death in humans with HCM,[75, 143–145] severe LV hypertrophy in cats may be associated with an unfavorable prognosis.[25, 39] Marked hypertrophy is present when the maximal LV free wall or interventricular septal thickness measured at end-diastole exceeds 8 mm. Accordingly, a number of drugs have been used as monotherapy in severely affected cats, but clinical benefit and comparative efficacy have not been established. Beta-blockers are often chosen for the following reasons:[75, 83, 146–149] (1) heart rate control (negative chronotropism) and associated indirect improvement of diastolic filling; (2) reduction of dynamic LV outflow tract obstruction; (3) reduction in myocardial oxygen utilization; (4) antiarrhythmic effects; or (5) ability to blunt sympathetic myocardial stimulation. Clinical reduction of resting heart rate to 120 to 160 beats/min is usually attainable with atenolol (6.25 to 12.5 mg q12–24h PO) or propranolol (5 to 10 mg q8 to 12h PO) for an average sized (4.5-kg) cat. Calcium channel blockers, most commonly verapamil, are often selected to improve LV relaxation and, therefore, diastolic filling, in human HCM.[150, 151] However, verapamil is rarely used in cats. Diltiazem is the safest and most frequently selected calcium antagonist in HCM cats. Rationale for use is based upon its actions promoting positive lusitropy, that is, to directly improve ventricular diastolic relaxation and filling.[13, 56, 57] Diltiazem may slow the heart rate in some cats but not in others, and heart rate reduction is much weaker than that resulting from β-blocker therapy. Several preparations of diltiazem are available: Cardizem tablets (Hoechst Marion Roussel), 7.5 mg q8–12h; Cardizem CD capsules, a long-acting formulation (Hoechst Marion Roussel), 10 mg/kg q24h; and extended release diltiazem (Dilacor XR, Rhone-Poulenc Rorer; each Dilacor XR 240-mg capsule contains four controlled-released 60-mg tablets, and the starting dosage is 30 mg q12–24h [some cats may tolerate 60 mg once to twice daily, although vomiting is a common side effect]). ACE inhibitors blunt neuroendocrine activation and may prevent deleterious cardiovascular remodeling. The merits of ACE inhibitors for treating feline HCM have a scientific basis,[147, 152–156] and ACE inhibitors have been used safely in the clinical setting.[156] Enalapril (0.25 to 0.5 mg/kg 24h PO) and benazepril (0.5 mg/kg q24h PO) are well tolerated.

SYNCOPE. Recurrent syncope is a risk factor for sudden death in humans with HCM[157–159a] and can be associated with tachyarrhythmias and bradyarrhythmias,[159] dynamic LV outflow obstruction,[160] altered baroreflexes,[161] and ischemia.[63] Moreover, syncope is usually distressing to owners of pets. In cats, syncope is most often clinically associated with physical activity or exertion and obstructive HCM. Exertional syncope in human HCM has been reported most often with the obstructive form.[75] Symptoms in humans have often been managed with negative inotropes (β-blockers, calcium antagonists [predominantly verapamil], and disopyramide) to alleviate or abolish dynamic LV outflow tract obstruction.[66, 74, 75, 148] In cats, there is little experience with verapamil, and disopyramide has not been studied. Beta-blockers are much more effective than diltiazem in reducing or abolishing dynamic LV outflow tract obstruction, associated pressure gradient, and syncope.

SPONTANEOUS ECHO CONTRAST ("SMOKE") AND STASIS. An echo phenomenon called *spontaneous echo contrast* is frequently observed in the LA or LV of cardiomyopathic cats and humans with certain cardiovascular diseases. Spontaneous echo contrast is associated with LA blood stasis. It is considered to presage thrombosis and is associated with increased thromboembolic risk (see Fig. 28–14).[162–164] The mechanism of spontaneous echo contrast has been attributed to erythrocyte aggregation at a low shear rate[165, 166] or platelet aggregates.[167, 168] Multiple interrelated factors may be involved in thrombogenesis, including blood stasis. Blood stasis within areas of ventricular akinesis or dyskinesis may provide a mechanism by which thrombi form.[169] Moreover, reduced LV contractility could precipitate left atrial blood stasis.[170] Concomitant mitral regurgitation (MR) has been associated with systemic platelet activation (presumably due to exposure to an

abnormal valvular surface or hemodynamic irregularity),[171] although severe MR may play a protective role in LV thrombus formation.[172] Given the many pathologic and hemodynamic derangements common to feline and human heart disease, spontaneous echo contrast and stasis should be considered a clinical marker for incipient thromboembolism and invoke a more aggressive therapeutic strategy (see Arterial Thromboembolism, later).

"MALIGNANT" FAMILY HISTORY (HIGH-RISK GENOTYPE). Pedigrees are occasionally identified in which a heritable pattern of HCM with severe morbidity and mortality is documented. For example, LV hypertrophy, heart failure, thromboembolism, and death have been reported in multiple generations of Maine coon cats,[39, 40] and other examples of familial transmission have been documented.[41] Thus, in related offspring, echocardiographic surveillance is warranted to evaluate disease progression, direct therapy, and assist prognosis. In such animals, early intervention with calcium channel blockers or β-adrenergic receptor blockers may be contemplated. Though unproved, this strategy is based on experimental and theoretical considerations which hold that a pathway to the phenotypic expression of LV hypertrophy is influenced by triggers such as higher LV pressure and workload,[105, 172a] conditions that might be ameliorated by certain pharmacotherapies. Implantable cardioverter-defibrillators have prevented sudden death in some human HCM patients. These have not been evaluated in felines.

MYOCARDIAL FAILURE. In some HCM cats, LV contractility is mildly to moderately reduced (e.g., fractional shortening, 23 percent to 29 percent; LV end-systolic dimension, 12 to 15 mm). This can result from acute or chronic myocardial infarction, particularly involving the LV posterior wall. Global LV failure has been observed, with diffuse LV necrosis and fibrosis. Occasionally, HCM progresses to a stage of chamber dilatation and systolic dysfunction resembling dilated cardiomyopathy. This is usually associated with refractory heart failure and poor prognosis. Oral taurine supplementation (250 mg q12–24h) is initiated whenever myocardial failure is detected, even if blood taurine cannot be immediately assessed (see discussion under treatment for systolic [myocardial] failure, later). An ACE inhibitor may be added for its beneficial effect to counteract neurohormonal activation and reduce deleterious remodeling. Digoxin may be administered (0.03 mg q48h) if contractility deteriorates, or if supraventricular tachyarrhythmias (particularly atrial tachycardia or atrial fibrillation) develop. Beta-blocker therapy might be beneficial if MI is suspected, or if a tachyarrhythmia warrants control of ventricular heart rate despite other therapies. Beta-blockers may also restore or "upregulate" β-adrenergic receptor numbers and sensitivity, protect myocytes from excess catecholamine levels, and blunt neuroendocrine activation.[173–175] One must be mindful of their potential negative chronotropic and inotropic effects, however. Therefore, a low starting dose of propranolol (2.5 mg q12h PO) or atenolol (3.15 mg q24h) may be initiated, followed by re-examination of heart rate by ECG and myocardial contractility by echocardiography.

TREATMENT OF SYMPTOMATIC CATS

CAUSES OF CARDIOVASCULAR EMERGENCIES. Most commonly, emergencies include left-sided heart failure (pulmonary edema), biventricular failure (pulmonary edema and effusions), or arterial thromboembolism; less commonly, tachyarrhythmias, syncope, pericardial tamponade, or systemic venous congestion (effusions) results. Renal and electrolyte abnormalities may be present.

EMERGENCY TREATMENT GOALS. Therapy for acute cardiovascular emergencies should (1) eliminate congestion (edema, effusions) and associated clinical signs; (2) suppress or abolish serious tachyarrhythmias; (3) improve ventricular relaxation and filling (diastolic function); (4) manage arterial thromboembolism and its consequences; and (5) eliminate syncope or exercise intolerance associated with dynamic LV outflow tract obstruction or tachyarrhythmia. In the severely dyspneic cat, care must always be taken to avoid stress.

Initial Therapy (First 24 to 48 Hours)

TREATMENT OF ACUTE PULMONARY EDEMA. Acute pulmonary edema is rapidly progressive and life threatening. Diuretics decrease preload and, thus, congestion. Accordingly, furosemide is administered (1.1 to 2.2 mg/kg PRN, usually q2–6h) and is individually adjusted to resolve dyspnea quickly. Peak diuresis occurs within 30 minutes of IV administration. Therefore, the first dose or two ideally should be administered by the intravenous route, followed by intramuscular injections until the pet is stable. These parenteral routes have superior bioavailability compared with oral administration. Furosemide inhibits renal tubular reabsorption of sodium and its accompanying anions and promotes diuresis. This reduces vascular volume, which decreases LV filling pressures (i.e., cardiac preload) and pulmonary edema.

Resolution of severe pulmonary edema may be enhanced by adding the preload reducer 2 percent nitroglycerin ointment (Nitro-Bid Ointment, Hoechst Marion Roussel; ¼ to ½ inch q6–8h cutaneously to the inside of the pinna) for the first 24 to 48 hours. Providing a 12-hour dose-free interval may reduce development of tolerance. Supplemental oxygen (40 percent

to 60 percent oxygen-enriched inspired gas) may be beneficial to improve pulmonary gas exchange.

Clinical improvement is indicated by the reduced respiratory rate and work of breathing, resolved auscultatory lung crackles, and clearing of alveolar infiltrates shown by radiography. The end-point of diuretic therapy is relief of clinical signs or progressive increase in blood urea nitrogen (BUN) and creatinine levels. Improvements in breathing should become noticeable within 2 to 6 hours after beginning furosemide, and continue. Clearing of pulmonary infiltrates (edema), as shown by radiography, is usually completed within 24 to 36 hours.[4, 5, 7] Cardiac responses to diuresis include decreased LA diameter and reduced Doppler echo transmitral E wave velocity.[89, 176]

Respiratory distress due to severe pleural effusion requires thoracocentesis. Pulmonary edema and pleural effusion often coexist, although pleural fluid hampers radiographic detection of edema. Dehydration and hypokalemia can result from overzealous diuresis, especially in the anorectic cat.[113a]

Chronic Maintenance Therapy

Chronic therapies are optimized to maintain cardiac compensation; prevent arterial thromboembolism; halt, slow, or reverse myocardial dysfunction (theoretically); promote enhanced quality of life; and prolong survival. Underlying conditions and risk factors (e.g., arterial hypertension, taurine-deficient diets, hyperthyroidism, anemia) are treated when identified.

DIURETICS. The goal of diuretic therapy is to ameliorate congestive signs. As soon as congestion is reduced and breathing improves, furosemide is changed from IV or IM to PO administration (typically, 6.25 mg q12–24h PO). This is then gradually decreased to the lowest effective dosage, which is highly individualized. Some cats remain stable on 1.1 to 2.2 mg/kg PO given every other day whereas in others, diuretics may be largely unnecessary and can be safely discontinued. In some cases, diuretics can be titrated expediently (typically by 1 to 2 mg/kg) to control dyspnea associated with recurrent pulmonary congestion or pleural effusion, thereby preventing hospitalizations. Compensatory hypertrophy of the distal nephron occurs in response to chronic loop diuretic therapy. Distal sodium resorption increases to overcome the intended clinical response to furosemide.[176a,b] As a result, diuretic resistance may occur as heart failure progresses, despite high doses of furosemide.[176a,c] Cats with advanced, chronic CHF presenting for acute exacerbations of congestion are likely to benefit from intravenous furosemide, which has higher bioavailability, or from combining two diuretics, such as a loop diuretic (furosemide) and a thiazide (see Recurrent and Refractory Congestive Heart Failure, later). It is always prudent to assess BUN, creatinine, and electrolytes in anorectic or decompensated cats receiving diuretics.[113a]

PHARMACOLOGIC OPTIONS AND APPROACHES TO CHRONIC MANAGEMENT. Whereas diuretics represent the traditional component of chronic heart failure management, other agents are selected to reduce diastolic dysfunction or its sequela. Beta-adrenergic receptor blockers have represented the traditional approach to improve cardiac performance since 1977.[4–7, 34, 35, 177, 178] The calcium channel blocking drug diltiazem first gained advocacy as a therapeutic strategy in 1991.[56, 57, 179] More recently, ACE inhibitors have been proposed as a third pharmacologic option.[156, 180] Although most clinicians tend to favor β-adrenergic blockers when tachycardia or dynamic LV outflow tract obstruction is present, there is a lack of consensus. Moreover, there are no data to indicate which is the optimal therapy for chronic management, whether combined therapy is more advantageous than monotherapy, or for that matter, whether therapy is significantly better than no therapy at all. Drugs are therefore administered on an empirical basis, relying on clinical experiences, preferences, and theoretical benefits. Accordingly, advantages and disadvantages for each therapeutic approach are discussed here.

BETA-ADRENERGIC BLOCKERS. The relationships between sympathetic nervous system activation and deleterious cardiovascular effects have been demonstrated in a number of human and animal models of cardiovascular disease, and these relationships provide a rationale for using β-adrenergic blocker therapy.[123, 181–192] Prolonged activation of the sympathetic nervous system may lead to cardiovascular injury that exacerbates disease progression,[173, 174] causes arrhythmias,[182] or stimulates vasoconstriction and secondary tissue anoxia.[175] Moreover, sustained vasoconstriction, elevated ventricular afterload, and a number of additional mechanisms contribute to abnormal cardiovascular remodeling and progression to congestive heart failure.[181, 183, 184] Left ventricular diastolic function is very sensitive to increases in sympathetic tone.[188] By decreasing heart rate, β-blockers prolong diastole and thereby increase passive ventricular filling and ventricular compliance. Prolonged diastolic filling allows more time for coronary blood flow and reduces myocardial ischemia.[186–188] In patients with heart failure, nonselective β-blockade may have favorable inhibitory effects on cardiac sympathetic activity.[187] These agents decrease myocardial oxygen requirements by reducing cardiac sympathetic stimulation, heart rate, left ventricular contractility, systolic myocardial wall stress, and systemic blood pressure.[185, 186] Dynamic LV outflow tract obstruction and related pressure gradient are often reduced or abolished.[74, 180] In addition, β-blocker therapy has decreased mortality in human clinical studies of myocar-

dial infarction and cardiac arrhythmias,[189, 190] and even at low doses, provided effective postmyocardial infarction therapy.[191] Beta-blockers also reduced all-cause mortality in humans with CHF.[193]

Propranolol and atenolol are the most commonly used β-blocking agents in cats. Propranolol (5 to 10 mg q8–12h PO) has been recommended for more than 25 years.[4-7, 34, 35, 177, 178] It improves clinical signs, reduces heart rate, decreases the severity of dynamic LV outflow tract obstruction, and is safe.[178, 180] A disadvantage is its need for frequent (tid) dosing because of its short half-life ($t_{1/2}$, 0.49 hour).[194] Moreover, propranolol has poor and variable oral bioavailability owing to extensive first-pass hepatic metabolism.[195] Recently, atenolol has become popular. It has high oral bioavailability (90 ± 9 percent), resulting in small interindividual kinetic variability; its $t_{1/2}$ is 3.66 ± 0.39 hours, and the heart rate attenuation following oral administration persists for at least 12 hours in normal cats.[196] Atenolol is dosed at 6.25 to 12.5 mg q12–24h PO. Adverse reactions to β-blockers are uncommon. Occasionally, lethargy or hypotension will occur, typically manifesting within an hour of initial oral administration. These effects quickly abate when the agent is discontinued.[5, 6, 180]

Despite these data, a number of important issues surrounding β-blocker therapy require clarification. The comparative advantages of β-blockers relative to morbidity and survival, when used to treat diastolic dysfunction, have yet to be validated by a large clinical trial. Furthermore, it is unknown whether the potential benefits of β-blockers vary with respect to stage of disease both within and between forms of cardiomyopathy, and clinical evaluations comparing various β-blockers have not been performed.

CALCIUM CHANNEL BLOCKERS. Since the dominant pathophysiologic abnormality in HCM is diastolic dysfunction, a rationale for using drugs that improve diastolic performance is self-evident.[13, 26a, 30, 56, 59] Calcium channel blockers exert cardiovascular effects that differ markedly among individual agents.[196a, b] Although clinical improvements have been reported after calcium antagonist therapy in some humans with HCM, most patients have been treated with verapamil,[30, 74, 148, 197-200] a drug used only rarely in cats.[56, 179] In general, calcium antagonists may reduce heart rate (verapamil much more so than diltiazem) and blood pressure, exert a mild, negative inotropic effect (reducing myocardial oxygen consumption), and improve rapid diastolic ventricular filling.[13, 56, 196a, b, 197-200] Verapamil improves cardiac symptoms and exercise capacity in many human patients with HCM.[197] This effect may be associated with a decrease in systolic function, improvement in diastolic relaxation and filling, and probably a reduction of myocardial ischemia.[196b, 198-200] Diltiazem has been studied in humans with HCM and appears to improve LV diastolic function,[200a-201a] although it is generally judged to be less efficacious than verapamil in cases of LV outflow obstruction.[74, 75, 143, 208]

In cats with HCM and pulmonary edema, one study compared the clinical effects of propranolol versus diltiazem in a small number of animals. The treatment group receiving diltiazem and furosemide (12 cats) realized improvements in pulmonary congestion, LV relaxation, and LV filling, although too few patients (5) were allocated to the propranolol group to make comparative assessment meaningful.[56] Regression of LV wall thickness was also reported to be a common treatment sequela of diltiazem therapy in this study, but such a phenomenon is regarded to occur only rarely.

The reported $t_{1/2}$ of conventional diltiazem (Cardizem, 1 mg/kg PO tid) in healthy cats was 113 ± 24 minutes; peak concentration following oral administration was achieved in 45 ± 36 minutes; and bioavailability was 50 percent to 80 percent. Clinically, this drug is dosed at 7.5 mg tid PO. A slow-absorption, long-acting diltiazem formulation (Cardizem CD, 10 mg/kg q24h) had a reported $t_{1/2}$ of 411 ± 59 minutes; peak concentration following oral administration was achieved in 340 ± 140 minutes; and bioavailability was 22 percent to 59 percent.[203] A disadvantage of the CD preparation is that it is currently available only in capsules, thus requiring formulation for dispensing. A third formulation (Dilacor XR) is available in extended release; each 240-mg capsule contains four controlled-release 60-mg tablets. Starting dose for a 5-kg cat is 30 mg q24h, and titration to 60 mg daily is tolerated in some cats.

Because myocardial infarction (MI) is a relatively common finding at necropsy in cats with myocardial diseases,[105] clinical experiences in the management of myocardial infarction in humans may be relevant. The use of calcium channel antagonists in post-MI human patients with LV dysfunction was not associated with a clinical improvement (i.e., reduction of subsequent cardiovascular events).[204] Other studies, however, showed a higher adverse cardiac event rate when calcium channel blockers were used.[205] Moreover, it is currently recommended that, for humans with myocardial infarction, heart rate–lowering calcium antagonists (e.g., verapamil, diltiazem) be reserved for patients without CHF in whom a β-blocker is contraindicated or in conjunction with an ACE inhibitor.[206] In fact, use of some calcium channel blockers in patients with left ventricular dysfunction was associated with increased risk of fatal or nonfatal MI,[136] possibly by activating the neuroendocrine system.[137] Thus, calcium antagonists are not currently recommended for routine secondary prevention after infarction.[207] Whether or not these data are relevant to treatment strategies for feline myocardial diseases remains to be determined.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS. Because neurohormonal activation plays an important role in heart failure,[208] disruption of neurohormonal activation should provide a therapeutic rationale for using ACE inhibitors.[209, 210] Clinical benefits, including relief of dyspnea, improvement in LV function, prevention of progressive ventricular dilation, and improved survival, have in fact been documented in humans with symptomatic heart failure or asymptomatic LV dysfunction following pharmacologic blockade of the renin-angiotensin-aldosterone system (RAAS).[210-213] Survival and quality of life were also improved in dogs with heart failure who were treated with enalapril.[214, 215] ACE inhibitors favorably alter hemodynamics in some humans with systolic dysfunction and reduce preload, afterload, and systolic wall stress, thereby increasing cardiac output without elevating heart rate.[216-218]

The rationale for ACE inhibitor therapy in the treatment of HCM can be argued based upon the salutary effects of these drugs on a number of cardiovascular factors. Pathologic features of HCM are related to systolic and/or diastolic dysfunction associated with LV hypertrophy and derangements of myocardial extracellular matrix.[13, 25, 26, 56, 55, 67, 219-221] The RAAS plays a prominent role in human HCM patients by influencing or regulating the expression of myocardial hypertrophy.[222] Furthermore, there is some evidence that the RAAS is activated in cats with HCM.[222a] Inhibition of the RAAS has a beneficial effect on extracellular remodeling in heart failure,[223] and ACE inhibitors reduce ventricular remodeling by blocking the tropic effects of angiotensin II on myocytes.[224, 225] Moreover, ACE inhibitors may improve LV diastolic function in hypertensive LV hypertrophy[226] and improve coronary hemodynamics.[227] Given the clear survival benefit provided by early use of ACE inhibitors in acute human MI,[227a] background therapy with ACE inhibitors theoretically might confer beneficial effects in similar circumstances. Recently, ACE inhibitors have been used to treat HCM in humans[228] and cats.[156] However, other investigators have highlighted the importance of the cardiac RAAS in development of LV diastolic dysfunction, LV subaortic obstruction, and decreased coronary flow reserves in human HCM patients. Selective inhibition of cardiac RAAS with ACE inhibitors or with angiotensin II receptor blockers might therefore lead to more favorable clinical outcomes.[229] This strategy has not been tested in cats.

Many clinicians add an ACE inhibitor (usually enalapril) to furosemide, combined with β-blocker or calcium channel blocker therapy, if right-sided heart failure is present, if pulmonary edema recurs, or if progressive atrial enlargement is detected. In a retrospective study without controls, enalapril added to standard therapies in 19 HCM cats resulted in a small but statistically significant reduction in LA dimension and interventricular septum and LV wall end-diastolic thickness.[156] Less commonly, an ACE inhibitor is used with or without furosemide as primary therapy for HCM. Enalapril (0.25 to 0.5 mg/kg q24h PO) and benazepril (0.25 to 0.5 mg/kg q24h PO) are clinically well tolerated,[156, 180, 230, 231] although data are limited concerning use of these agents in cats. After oral administration of enalapril dosed at 0.25 and 0.5 mg/kg, a 95 percent reduction in ACE occurred between 2 and 4 hours after either dose, and it remained depressed to less than 50 percent of control for 2 to 3 days.[230] After single doses of benazepril (0.5 mg/kg), peak plasma benazeprilat levels were achieved 2 hours after oral administration, and over 90 percent of plasma ACE inhibition persisted at 24 hours.[231]

A number of clinically important aspects of ACE inhibitor therapy in feline HCM remain to be determined, including the optimal timing for ACE inhibitor administration, the most effective dosage, and the effects of these agents on morbidity and mortality. Moreover, individuals who could optimally benefit from ACE inhibitor therapy have not been identified. For example, in one human cooperative heart failure trial, the most beneficial response to ACE inhibition occurred in patients with the most neurohumeral activation.[232] It has not been determined which ACE inhibitors best exert selective cardiac RAAS blockade at doses that do not affect cardiac loading conditions. Enalapril has low affinity for cardiac tissue ACE, whereas benazepril and others have higher affinity, but the clinical importance of this is unknown. ACE inhibitors reduce blood pressure, which theoretically could be deleterious in HCM cats with severe LV outflow tract obstructions or syncope, although such untoward effects have not been reported.

REDUCTION/ELIMINATION OF LV OUTFLOW TRACT GRADIENT (SAM). Negative inotropic drugs that reduce or eliminate obstruction have been widely used in humans with the obstructive form of HCM. These agents have included disopyramide, β-adrenergic blockers, or calcium channel blockers (principally verapamil).[74, 233, 234] Drug selection is not standardized. In cats, pharmacologic management has been generally confined to the use of β-adrenergic blockers (atenolol, propranolol) and calcium channel blockers (principally diltiazem), but reduction of outflow gradient is usually best accomplished with β-blocker therapy. Stimuli that provoke or intensify LV outflow tract gradients should be avoided. These include positive inotropes, reduction of LV volume, or decreased afterload. Conversely, the gradient may be reduced or abolished by interventions that increase LV volume, such as decreased contractility, increased preload, or increased afterload. The clinical importance of decreasing obstruction, particularly in asymptomatic cats, has not been established.

Recurrent and Refractory Congestive Heart Failure

When pulmonary edema or biventricular failure with pulmonary edema recurs, emergency treatment may be required (see earlier Treatment of Acute Pulmonary Edema). Cardiac drug therapy is then modified to (1) increase the dosage of the "primary" drug (i.e., β-blocker, calcium channel blocker, or ACE inhibitor), (2) change to a different class of primary drugs, or (3) add a second or even third primary agent. When congestion is refractory to these pharmacologic manipulations, particularly with severe, chronic effusions, upward dose titration of furosemide (e.g., 2.2 to 4.4 mg/kg q8–12h PO) may be required. For refractory right-sided heart failure, addition of a second diuretic agent that acts at a different site in the nephron may be synergistic with furosemide. Choices for these agents include hydrochlorothiazide (HydroDiuril, Merck & Co.; 1 to 2 mg/kg PO q12–24h PO) or hydrochlorothiazide-spironolactone (Aldactazide, Searle; 2.2 mg/kg/day PO).[113a] Cats must be closely monitored for dehydration, azotemia, hyponatremia, and hypokalemia when using combination diuretics.

Digitalization may be prescribed when right-sided heart failure is unresponsive to diuretics, ACE inhibitors, or other therapy; or if myocardial (systolic) failure occurs. If renal function is relatively normal, digoxin may be administered. The tablet form (0.125 mg) is generally better tolerated than digoxin elixir. Guidelines for oral digitalization are as follows: cats weighing 1.9 to 3.2 kg, ¼ tablet (0.031 mg) every second day; cats weighing 3.3 to 6 kg, ¼ tablet daily; and cats weighing more than 6 kg, ¼ tablet daily or q12h. This maintenance dose is highly individualized and may need to be reduced to account for weight loss (cardiac cachexia), renal insufficiency, and hypokalemia.[5, 7] Dosage is titrated by assessing serum digoxin concentration in 10 to 14 days (1 to 2 ng/ml represents a therapeutic range).

For continued refractory CHF, several additional steps should be taken: (1) ascertain that prescribed drugs are being administered according to directions, (2) recalculate drug doses based on current body weight, (3) generate and re-evaluate a new data base (e.g., ECG, radiographs, echocardiogram, clinical pathology) to rule out systemic and metabolic disease, heartworms, neoplasia, (4) assess serum T_3 and T_4 concentrations (cats > 6 years old), and (5) refer the animal to a cardiologist.

RESTRICTIVE CARDIOMYOPATHY

DEFINITIONS AND NOMENCLATURE

Restrictive cardiomyopathy (RCM) is defined as heart muscle disease that results in impaired diastolic ventricular filling: normal or decreased ventricular diastolic volume; generally normal systolic function; and normal to increased ventricular wall thickness.[3] It represents a spectrum of conditions in humans that includes idiopathic RCM and RCM that occurs secondary to systemic or metabolic disorders that affects the ventricles. These different etiologies result in a variety of clinical and morphologic phenotypes, pathophysiologic derangements, and diastolic dysfunction.[1–3, 9, 14, 236–252] Thus, the only justification that can be made to describe a given case of myocardial disease by the term "restrictive cardiomyopathy" is that the case should be characterized by a cardiomyopathic process that restricts diastolic ventricular filling and excludes hypertrophic cardiomyopathy. Accordingly, RCM is a specific pathophysiologic entity characterized within a broader group of conditions that cause diastolic dysfunction or diastolic heart failure.[249, 252] Two basic categories of RCM are recognized in humans,[1–3, 8, 8a, 14, 236–238, 247–252] and these appear to be valid for cats as well.[4–7, 9, 239–242] They include (1) *myocardial RCM* (most prevalent) and (2) *endomyocardial RCM.*

PREVALENCE AND DEMOGRAPHICS

Prevalence data (see Fig. 28–1) have been complicated by controversies in clinical diagnosis and antemortem recognition. There are no known gender or breed predilections. Ages of affected cats are variable, but middle-aged or older animals are most commonly affected.[239, 242]

ETIOLOGY

Both myocardial and endomyocardial forms of feline RCM are idiopathic. The myocardial form is poorly characterized in cats but is generally a noninfiltrative disease. In humans, this form of RCM most commonly results from amyloid infiltration of the ventricular walls,[1, 2, 8, 8a, 235, 237] although other etiologies have been reported.[8] A familial form of idiopathic myocardial RCM has also been documented, both with[252, 253] and without[254] skeletal myopathy, in humans but currently not in cats.

Endomyocardial feline RCM has been associated with endomyocarditis of undetermined origin in a small number of cases.[242] Thus, it is possible that myocarditis is a causal factor of endomyocardial disease. The ability of many viruses to infect and potentially injure myocardial tissue and activate the immune system has been suggested as a cause.[255–259] Recently, isolation of parvoviral genomic material from a high percentage of feline hearts with idiopathic cardiomyopathy, including RCM,[260] gives credence to a similar mechanism in cats. Viruses may cause myocardial injury by several basic mechanisms, including direct myocardial invasion production of myocardial toxins, or

immune-mediated myocardial injury.[261] An etiopathogenic role of viral myocarditis has been suggested in some human patients who have residual cardiac injury that progresses to chronic myocardial damage and dysfunction.[262] Although the endomyocardial form of feline RCM is characterized by endomyocardial fibrosis, other conditions may potentially cause infiltrative endomyocardial disease, including metastatic neoplasia,[4–6] particularly lymphoma, which was detected in 3 percent of cats with lymphosarcoma.[262a] The endomyocardial form of human RCM and eosinophilic cardiomyopathy (Löffler's endocarditis) are thought to be different manifestations of restrictive obliterative cardiomyopathy associated with eosinophilia.[263] In cats, eosinophilic cardiomyopathy has not been described per se, although hypereosinophilic syndrome with multiorgan eosinophilic infiltration, including the heart, has been reported.[243, 245] Thus, a possible pathogenic relationship between direct eosinophilic involvement or indirect immune-mediated injury is speculated for some cases.

PATHOPHYSIOLOGY

The hallmark of RCM is diastolic dysfunction. Early LV filling is rapid but is then suddenly restrained, impeded by rigid ventricular walls or endocardium that impairs myocardial elasticity.[1, 14, 29] This results in elevated filling pressures, with resultant pulmonary and systemic congestion. Contractility (systolic function) is generally normal or only mildly impaired.

PATHOLOGY

MYOCARDIAL FORM (NONINFILTRATIVE, IDIOPATHIC) OF RCM. In humans, RCM most often results from systemic or metabolic processes that infiltrate the interstitial matrix. Amyloid is the most common cause, although accumulation of metabolic storage material within myocytes also occurs.[1, 8, 237]

Although RCM is poorly characterized in cats, neither amyloid infiltration nor deposition of abnormal metabolic material within myocytes has been identified. Thus, the feline condition represents a noninfiltrative, idiopathic RCM. Gross pathologic features include mild to moderate increase in heart weight and heart weight to body weight ratio; increased biatrial size with particularly severe LA enlargement; relatively normal LV internal cavity size; and normal to mildly increased LV wall thickness (Fig. 28–15). Patchy endocardial fibrosis is common. Ball thrombi may be present in the LA or LV. Common histopathologic findings include diffuse or patchy interstitial fibrosis and myocyte necrosis.

ENDOMYOCARDIAL FORM OF RCM. Two forms of endomyocardial RCM—endomyocardial fibrosis and hypereosinophilic syndrome (Löffler's endocarditis)—have

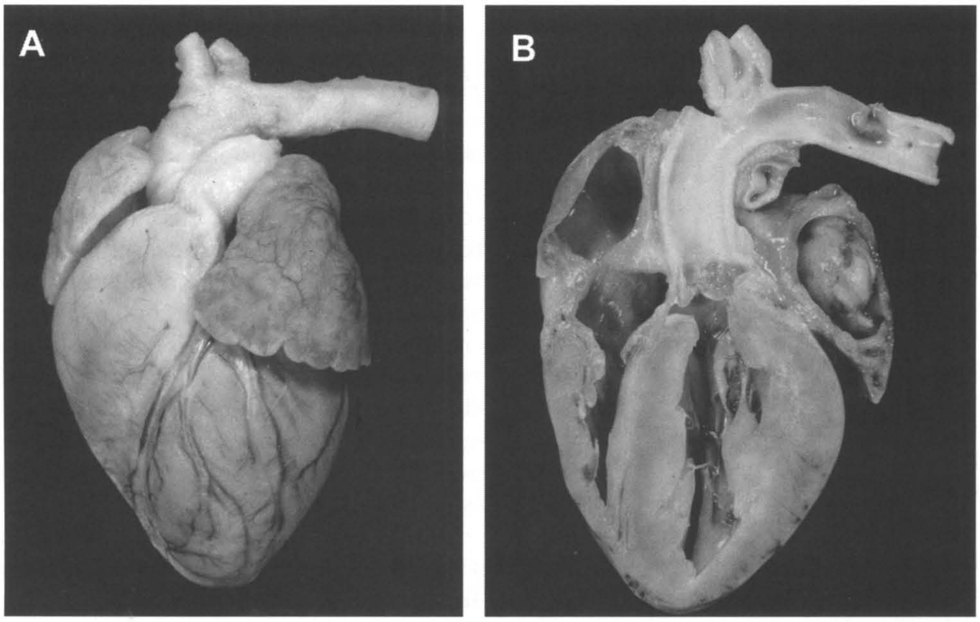


FIGURE 28–15

Heart from a cat with the myocardial (noninfiltrative) form of idiopathic restrictive cardiomyopathy. (A) There is biatrial enlargement. Left auricular dilation is striking. (B) Transverse section of this heart reveals mild RV hypertrophy, RA enlargement, and a left auricular ball thrombus. Although the ventricular septum and LV free wall appear thickened, this appearance is due to contiguous regions of sectioned papillary muscles adjacent to the septum and free wall, which resulted from the oblique transection of this gross specimen. Echocardiographic examination had revealed normal left ventricular internal dimensions and ventricular septal and LV free wall thickness.

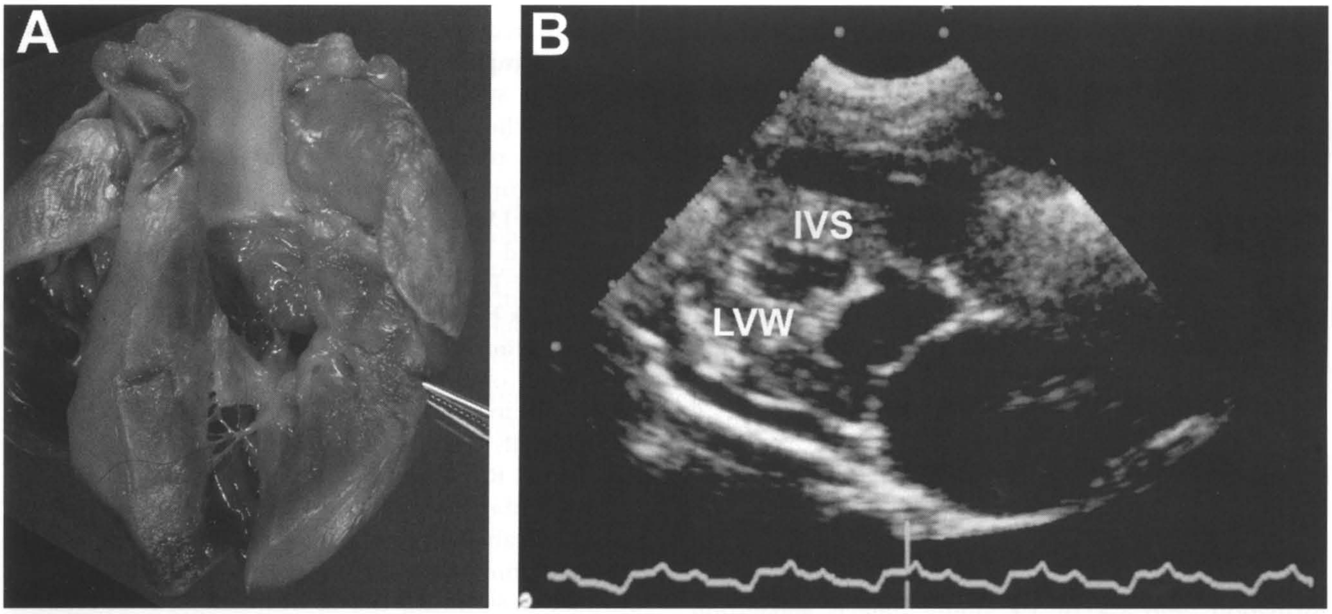


FIGURE 28–16

Heart from a cat with the endomyocardial form of restrictive cardiomyopathy. The transected heart (A) and the two-dimensional parasternal long axis echo (B) reveal a large mid-ventricular endocardial scar bridging the interventricular septum and left ventricular posterior wall. The left atrium is severely enlarged and mild pericardial effusion is present. *IVS,* interventricular septum; *LVW,* left ventricular posterior wall.

received the most attention in humans. They may represent different manifestations of the same disease and are associated with an eosinophilic cardiomyopathy. It has been hypothesized that activated eosinophils cause myocardial toxicity,[264] a theory supported by animal models of hypereosinophilic syndromes.[242, 243, 265, 267] A feline hypereosinophilic syndrome (HES) has been reported. In a single cat with HES, the echocardiogram was unremarkable, but focal mononuclear cell infiltration was present within the myocardium.[243] In another report of feline HES in 3 cats, 2 were necropsied and had subendocardial eosinophilic infiltration without fibrosis or gross cardiac lesions.[245] In the endomyocardial form of feline RCM, endomyocarditis and LV endomyocardial fibrosis have been reported occurring both separately and together.[9, 141, 242, 266]

Gross pathologic findings (see also chapter 36) (Fig. 28–16) include greater than normal heart weight and heart weight to body weight ratio; severe LV endocardial scar (typically in the mid to apical cavity) often obliterating the distal chamber, causing midventricular stenosis or fusing and distorting the mitral apparatus; normal to hypertrophied LV wall; severe LA and often RA enlargement; MI; variable RV changes, including hypertrophy; and LA or LV mural ball thrombi. Histologic findings include marked LV endocardial thickening and scar; intramural coronary arteriosclerosis; endomyocardial necrosis and fibrosis; and in cases of LV endomyocarditis, varying degrees of endomyocardial infiltrates, predominantly neutrophils and macrophages but occasionally lymphocytes and plasma cells.

CLINICAL MANIFESTATIONS

HISTORY. Tachypnea and dyspnea may be acute or subacute, with pulmonary edema. In chronic stages of the disease, effusions may predominate and cause gradual signs of dyspnea and weight loss associated with cachexia. Anorexia may precede respiratory involvement. Aortic thromboembolism is common and results in paresis.[237]

PHYSICAL EXAMINATION. Findings are nonspecific. Dyspnea and tachypnea are usually evident. Thoracic auscultation may reveal dull heart and lung sounds in the presence of marked pericardial or pleural effusion, or respiratory crackles may be evident if severe pulmonary edema is present. Soft, systolic heart murmurs may be detected over the mitral or tricuspid valve area or between the mitral valve area and sternum. Gallop heart rhythms are sometimes present. Distended jugular veins and elevated jugular venous pressures are associated with right-sided CHF. Irregular heart rates and arterial pulse deficits indicate arrhythmias. Arterial thrombosis predisposes to saddle thrombi and posterior paresis.

ELECTROCARDIOGRAPHY. Arrhythmias are common (see Table 28–2). A variety of ECG changes may be recorded. Low voltage QRS complexes may be noted when severe pericardial and pleural effusions are present. Evidence of LA enlargement (P wave duration >

40 msec) or LV enlargement (R_{II} > 0.8 mV or QRS duration > 40 msec) is common.

RADIOGRAPHY. Classic radiographic changes include moderate to severe LA enlargement and, often, RA enlargement. Pulmonary edema and pleural effusion are common. Generalized cardiomegaly may be evident if pericardial effusion is present. Ascites is occasionally present, especially in cases of chronic disease.

ANGIOCARDIOGRAPHY. Although echocardiography has largely replaced nonselective angiocardiography for cardiac imaging, the latter may be informative, particularly with RCM due to endomyocardial fibrosis (Fig. 28–17). Angiographic findings include severe LA enlargement; an irregular LV cavity, often with partial midventricular constriction or striking obliteration of the apical cavity caused by severe endocardial scar formation; and LA or LV filling defects suggesting intracavitary ball thrombi. The noninfiltrative myocardial form of RCM is characterized by severe LA enlargement with a relatively normal-appearing LV cavity. Ball thrombi may also be present. Right-sided changes are variable with both forms.

ECHOCARDIOGRAPHY. The endomyocardial and myocardial forms of RCM can generally be distinguished by echocardiographic examination. The cardinal features of endomyocardial RCM include (1) pronounced endocardial scar, most commonly at the level of the mid left ventricle, bridging the free wall and ventricular septum (see Fig. 28–16); this may cause mild to severe midventricular constriction, resulting in a diastolic and systolic pressure gradient identifiable by Doppler echocardiography; and (2) severe LA enlargement with pronounced left auricular dilation. Additional features are usually present. The ventricular septum or LV posterior (free) wall may be mildly hypertrophied (e.g., end-diastolic thickness 5 to 6 mm) or normal. The LV posterior wall may appear nonhomogeneous because of focal hyperechoic areas or diffuse speckling. Left ventricular cavity dimensions may be normal or reduced, or severe endocardial fibrosis may result in obliteration of the apical LV cavity. The RA is usually enlarged. Right ventricular changes vary from mild RV hypertrophy to dilation. Intracavitary ball thrombi (LA or LV) are common. Mitral and tricuspid valvular insufficiency is often present, but regurgitation is usually mild. Contractility is generally normal. In contrast, the myocardial form of RCM is characterized by (1) marked LA or biatrial enlargement, (2) a relatively normal LV chamber, (3) normal ventricular septum and LV free wall thickness or mild hypertrophy (end-diastolic wall dimensions 5 to 6 mm), and (4) lack of severe, left-sided heart volume overload (i.e., valvular insufficiency, if present, is mild).

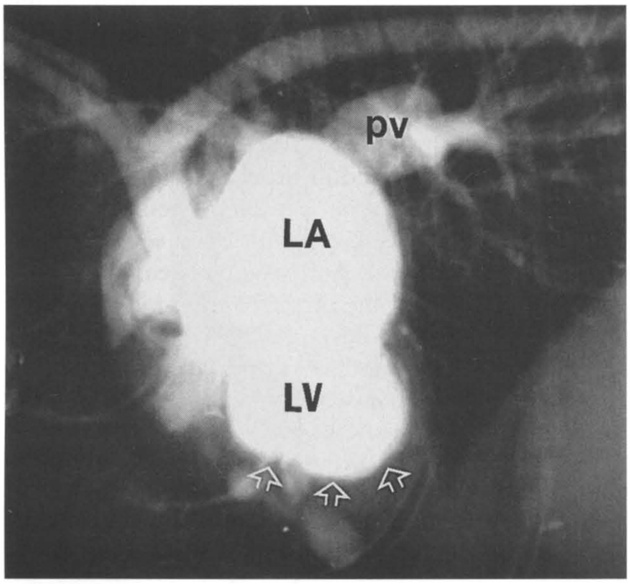


FIGURE 28–17

Nonselective angiocardiogram of a cat with restrictive cardiomyopathy (RCM). The left atrium (LA) is dilated and the left ventricular chamber is misshapen *(arrows)*. (From Fox PR, Bond BR. Nonselective and selective angiocardiography. Vet Clin North Am 13:262, 1983.)

DIFFERENTIAL DIAGNOSIS

From a pathophysiologic perspective, the diagnosis of RCM requires either Doppler echocardiographic evidence of LV restrictive physiology or LV relaxation abnormality, in the absence of severe idiopathic LV hypertrophy. When Doppler echo evidence of diastolic dysfunction is lacking, a presumptive diagnosis of RCM is based upon cardiac morphology that closely conforms to classic phenotypes of RCM (see preceding Echocardiography) and excludes HCM, myocardial infarction, and other cardiomyopathies. Thus, RCM is diagnosed from the presence of a number of structural and physiologic features and by the absence of others. A diagnosis of RCM is not tenable in the presence of significant left ventricular dilation. Likewise, severe LV hypertrophy, particularly without LV endocardial scar, is incompatible with a diagnosis of RCM.

Restrictive cardiomyopathy causes a syndrome that is hemodynamically similar to constrictive pericarditis, an exceedingly rare condition in cats. Abnormalities of diastole in RCM and HCM do share some similarities, and thus the clinical picture may be confusing. Both RCM and HCM may present with acute pulmonary edema, arrhythmias, and severe LA or biatrial enlargement; moreover, some RCM cases have equivocal LV hypertrophy or myofiber disorganization. Most commonly, the diagnosis of RCM is somewhat uncertain. In many cases, myocardial diseases may be more appropriately labeled *unclassified cardiomyopathy* if they are equivocal, have marked mitral regurgitation and

LA enlargement, have only mild LA enlargement, or have normal Doppler echo transmitral filling patterns.

NATURAL HISTORY AND PROGNOSIS

The true natural history of RCM is difficult to determine, since asymptomatic cardiomegaly may be present for months or years. The rate of progression of diastolic dysfunction has not been determined. Frequently, RCM has an insidious onset, with development of progressive right-sided CHF. Prognosis is generally poor when marked right-sided CHF is present, especially when accompanied with tachyarrhythmias such as atrial fibrillation.

THERAPY

Acute therapy for pulmonary edema is similar to that described earlier for hypertrophic cardiomyopathy. When moderate to severe pleural effusion is present, therapeutic thoracocentesis may be helpful. There are currently no clinical data indicating optimal chronic management of restrictive cardiomyopathy. Consideration may be given to ACE inhibitors, with the rationale for blunting neurohormonal activation and reducing ventricular remodeling; to β-blockers, particularly when myocardial infarction is suspected or tachyarrhythmias are present; or to aspirin when left atrial enlargement is severe. Digoxin can be considered for severe or refractory right-sided CHF.

SYSTOLIC (MYOCARDIAL) DYSFUNCTION

TAURINE DEFICIENCY, DILATED CARDIOMYOPATHY, AND IDIOPATHIC MYOCARDIAL FAILURE

DEFINITIONS AND NOMENCLATURE

When the ventricles fail to generate normal systolic contractile force to maintain forward cardiac output, *systolic dysfunction* is said to be present. Synonymous terminology includes *myocardial failure, pump failure, systolic failure, contractile dysfunction,* and *reduced contractility.* Dilated cardiomyopathy is the prototypic example of systolic dysfunction. It is characterized by LV or biventricular dilatation and impaired contractility.[3] Although formerly called *congestive cardiomyopathy,* the term *dilated cardiomyopathy* is preferred, because ventricular dilation and decreased contractility represent the earliest abnormalities, whereas CHF often develops later.[1, 2]

PREVALENCE AND DEMOGRAPHICS

Historically, dilated cardiomyopathy (DCM) had represented the second most common form of feline heart disease (see Fig. 28–1). At The Animal Medical Center, it accounted for about one quarter of necropsy-confirmed cardiomyopathies between 1962 and 1976,[9] and for up to 30 percent of primary myocardial diseases diagnosed by echocardiography before 1990. Ages of cats with taurine deficiency DCM varied from 5 months to 16 years, with a mean age of approximately 7.5 years.[35, 141] All breeds were affected. An apparently high incidence occurred in the Siamese, Abyssinian, and Burmese breeds[5, 7] and a relatively low incidence in the Himalayan and Persian breeds. There was a male predisposition.

However, in 1987 an association between taurine deficiency and reversible myocardial failure (DCM) was reported[268] and subsequently corroborated.[269–280] In response, pet food manufacturers reformulated their feline diets to include more taurine, which resulted in a dramatic reduction of feline taurine deficiency in the northeastern United States by 1990. Similar epidemiologic trends were reported elsewhere.[281]

The clinical relationship between taurine deficiency and systolic dysfunction was evaluated in 49 cats diagnosed with idiopathic myocardial failure between 1990 and 1995. Ages ranged from 2 to 20 years (mean, 9.8 ± 4.4; median, 9.5 years); 69 percent were male and 31 percent were female. Five cats (10 percent) had markedly reduced taurine concentrations, and their clinical condition was compatible with taurine deficiency DCM. An additional 10 cats (20 percent) had somewhat reduced whole blood taurine concentrations compared with normal.[282]

Currently, idiopathic myocardial failure represents from 3 percent to 7 percent of the cardiomyopathic cats evaluated at The Animal Medical Center for suspected heart disease. A wide variation occurs in degree of systolic impairment and left ventricular morphology.

ETIOLOGY

TAURINE DEFICIENCY MYOCARDIAL FAILURE. A clear causal relationship has been demonstrated between deficiency of the amino acid taurine and reversible feline myocardial failure.[268, 275–278] Prior to 1987, most cases of DCM were apparently related to consumption of commercial cat foods that either had an inadequate taurine content,[275] or whose taurine was rendered unavailable due to processing and canning.[277] However, it is not certain that taurine deficiency alone is the only factor responsible for the development of myocardial failure. For example, many cats fed taurine-deficient diets for prolonged periods of time failed to develop clinical myocardial failure; clinical disease is not consistent or predictable; the clinical incidence of DCM in

cats consuming commercial diets implicated in taurine deficiency was low; and myocardial taurine concentrations in taurine-depleted cats do not readily indicate those that will develop myocardial failure.[269, 271] In addition, certain breeds appeared to be at greater risk of developing taurine deficiency myocardial failure, including the Abyssinian, Siamese, and Burmese breeds,[5, 7] and a genetic predisposition to feline DCM has been reported.[263] Nevertheless, the incidence of myocardial failure (i.e., DCM) became dramatically reduced after commercial pet food companies reformulated feline diets with fortified taurine contents. Although taurine deficiency DCM is still encountered,[262] it has remained a relatively rare cause of feline heart failure.

IDIOPATHIC MYOCARDIAL FAILURE. This category encompasses most cats diagnosed with myocardial failure since 1990 and is probably associated with more than one disorder. Etiologies are elusive. Pathogenesis of human idiopathic DCM represents a common expression of myocardial injury caused by a number of poorly understood myocardial insults.[1] Three basic mechanisms of myocardial damage include (1) genetic and familial causes,[284, 285] (2) viral myocarditis and other cytotoxic factors,[286–288] and (3) abnormalities of cellular and humeral immunity.[289, 290] A variety of other causes, including energetic, metabolic, and contractile abnormalities, have been proposed.[1, 2, 289] Some cats have had prominent myocardial fibrosis and infarction,[282] and familial transmission has been reported.[283] The possibility that myocarditis is associated with at least some cases of feline DCM is suggested by the isolation of parvoviral genomic DNA from myocardial tissues of cats with DCM.[260]

PATHOPHYSIOLOGY

When the LV fails to generate normal contractile force and ejection fraction is severely reduced, end-systolic and end-diastolic ventricular volumes increase and myocardial wall tension becomes elevated. Alterations in LV relaxation and diastolic compliance coexist with impaired contractile function and contribute to elevated filling pressure.[291, 292] Coronary flow reserve is decreased and is significantly correlated with LV function as assessed by LV end-diastolic pressures, end-diastolic volume and wall stress, and ejection fraction.[293] Activation of the sympathetic and RAAS further increases cardiac preload and afterload. End-systolic volume increases as a result of impaired LV contractility. Left ventricular end-diastolic, LA, and pulmonary artery wedge pressures are usually elevated. With RV dilation and failure, RV end-diastolic, RA, and central venous pressures may be elevated as well.[1] Congestive heart failure results from both depressed contractility and failure (or overcompensation) of neuroendocrine and other compensatory mechanisms. Pulmonary congestion, effusions, and signs of low cardiac output results, and cardiogenic shock may occur if global cardiac dysfunction is severe. Mild mitral insufficiency and occasionally tricuspid insufficiency are usually present, probably owing to the atrioventricular valve apparatus distortion that accompanies severe dilation. The degree of myocardial failure is variable, and prognosis is not always directly related to indices of contractility.

TAURINE DEFICIENCY CARDIOMYOPATHY. Although this etiology is currently rare in cats eating commercial cat foods, the potential for developing taurine depletion currently exists under several circumstances. Urinary acidification combined with potassium depletion may reduce tissue stores of taurine.[294] Taurine deficiency can also result when inappropriate diets are fed.[263, 268, 295, 296] Taurine is an essential dietary amino acid for cats due to their limited ability to synthesize taurine from cysteine and methionine. This is associated with a low concentration of cysteine-sulfinic acid decarboxylase, an enzyme required in taurine biosynthesis.[297, 298] Cats are unable to conjugate significant amounts of bile acids with glycine and therefore must utilize taurine for conjugation. Thus, under conditions of taurine depletion as may occur with inadequate dietary taurine, cats lose taurine in the bile, creating severe whole body taurine loss.[299, 300] Taurine is essential for normal structural and functional integrity of the tapetum and heart and for maintenance of normal reproductive function.[268, 301–303] Taurine deficiency is a major factor in the pathogenesis of taurine deficiency myocardial failure, a syndrome that is largely reversible by oral taurine supplementation.[268, 279]

PATHOLOGY

The chief morphologic feature of classic taurine deficiency DCM is dilation of all four cardiac chambers. Heart weights are significantly increased, ventricular walls are normal or thin, papillary muscles and trabeculae are atrophied, and aneurysmal thinning of the LV apex may be present. Focal LV endocardial fibrosis may be observed. Diffuse or focal myonecrosis may be present. Cardiac myocytes display various degrees of degeneration ranging from coagulation, granulation, and sarcoplasmic vacuolization to myocytolysis.[9, 21, 24, 35–37, 141] Gross features of idiopathic myocardial failure are more variable (Fig. 28–18). There is generally biatrial enlargement with or without hypertrophy. The LV is dilated, and the apex may be thinned. The ventricular septum may be thin or normal, and thinning of the LV free wall is common, typically occurring in the posterior segment of free wall as viewed in cross-section. The RV may be dilated, and the RV free wall may be thickened or thinned. Myocytolysis and necrosis, fibrosis, and intramural cor-

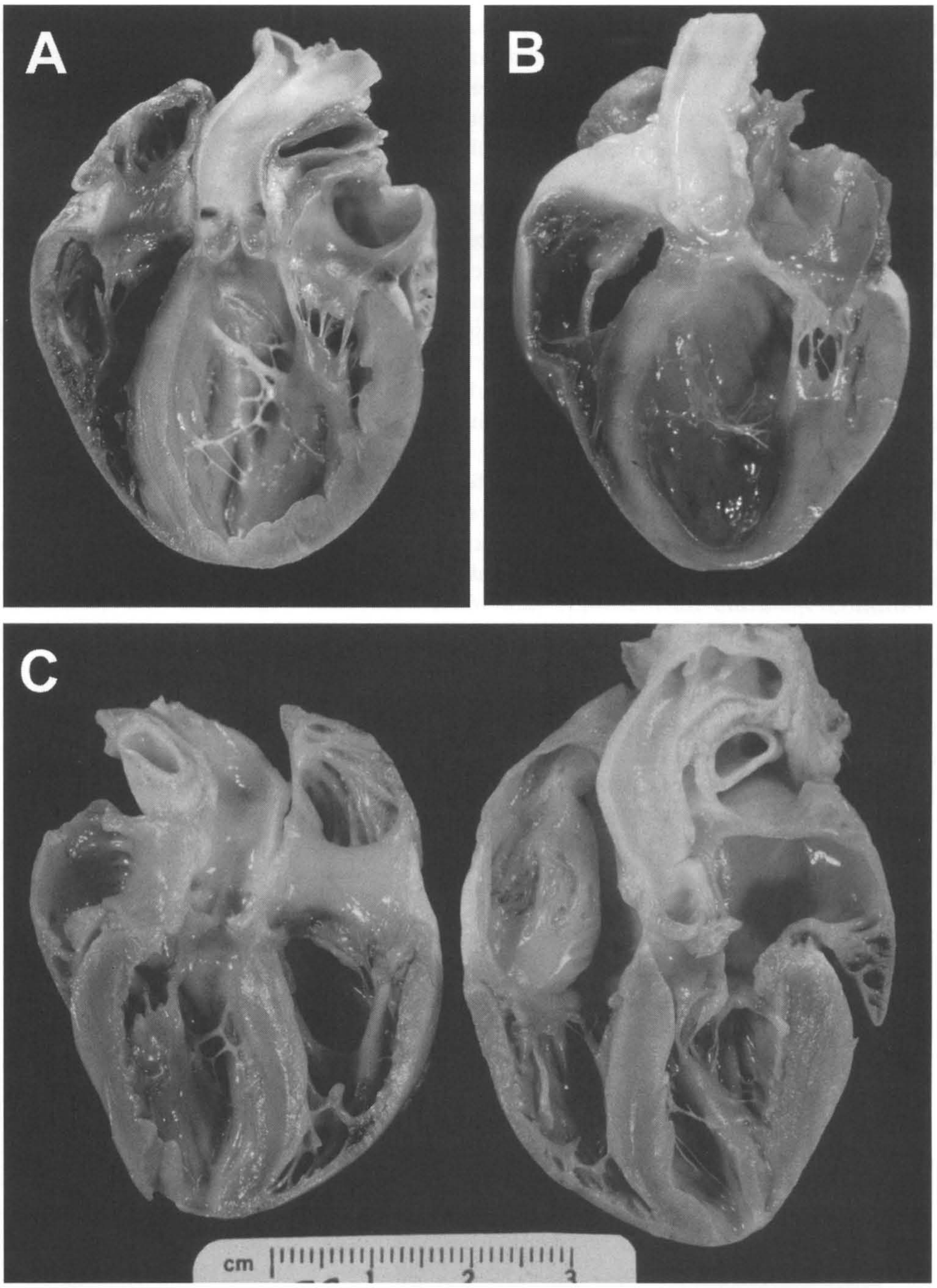


FIGURE 28–18

Gross heart specimens from three cats with idiopathic myocardial failure. Left ventricular contractility was severely depressed in cats A and B (fractional shortening <14 percent) and was mildly depressed (FS, 25 percent) in cat C. (A) Severe biventricular dilatation is present. The ventricular septum is thin but the LV free wall thickness is normal. Both atria are moderately enlarged. Abnormal moderator bands are present in the left ventricle. (B) Both ventricles are markedly dilated. The RV has segmental thinning and the LV apex is moderately thin. The interventricular septum is thin and pale. These pale regions corresponded to histological evidence of severe necrosis and replacement fibrosis. Papillary muscles are fused and flattened. Moderate biatrial enlargement is present. (C) There is severe biatrial dilation and the right ventricle is moderately enlarged (compare this with Fig. 28–22). The LV chamber is mildly dilated but the ventricular septal and LV free wall thickness are normal. The LV apex is very thin and measured 0.5 mm. The myocardial disorders in cats A and B were classified as dilated cardiomyopathy, whereas C was described as unclassified cardiomyopathy with mild myocardial failure.

onary artery remodeling (arteriosclerosis) are common. Ball thrombi may occur in the LA or LV.[282]

CLINICAL MANIFESTATIONS

HISTORY. Clinical signs are usually vague and most commonly include anorexia, dyspnea, and lethargy. Vomiting is commonly reported from 1 to 3 days prior to presentation. Paresis of a front or rear leg results from acute arterial embolization.[4–7, 282] This has been recorded in approximately one fifth of cats with idiopathic myocardial failure diagnosed during the past 6 years.

PHYSICAL EXAMINATION. Lethargy, depression, dehydration, and hypothermia frequently present. Gallop rhythms (presumably S_3) have been reported in 20 percent to 67 percent; a 2 to 3/6, systolic heart murmur heard over the left apex, sternum, or right apex is reported to occur in about 20 percent to 42 percent of affected cats.[4–7, 34, 35, 37, 292] Congestive heart failure at the time of presentation is common and was detected in 94 percent of cats with idiopathic myocardial failure.[282] In such cats, lung sounds may reveal crackles from pulmonary edema, or heart and lung sounds can be muffled if significant pericardial or pleural effusion is present. Jugular veins may be distended or pulsatile.

Hydroperitoneum and hepatomegaly can accompany pericardial and pleural effusion if right-sided heart failure is advanced. Central retinal degeneration is a common feature of severe taurine deficiency[268, 303] and persists even when whole body taurine has been restored to normal.

ELECTROCARDIOGRAPHY. The ECG is often abnormal (see Table 28–2). Changes may include widened P waves (P mitrale), indicating LA enlargement; tall R waves or widened QRS voltages, indicating LV enlargement; or various arrhythmias. Ventricular extrasystoles and short paroxysms of ventricular tachycardia are most common and have been recorded in 40 percent to 50 percent of DCM cases. Low-voltage R waves may indicate severe pericardial or pleural effusion.[4–7, 35, 37] First-degree atrioventricular block is a common conduction abnormality[34, 109, 110] and was recorded in 35 percent of cats with idiopathic myocardial failure.[271]

RADIOGRAPHY. Characteristic changes include generalized cardiomegaly and pleural effusion (Fig. 28–19). The latter may silhouette the cardiac shadow. Pulmonary venous congestion or mild, patchy pulmonary edema may be present concurrently but is often obscured by effusion.[4–7, 34, 35] In a series of 49 cats diagnosed between 1990 and 1995, pleural effusion was present in 71 percent and pulmonary edema in 22 percent.[282]

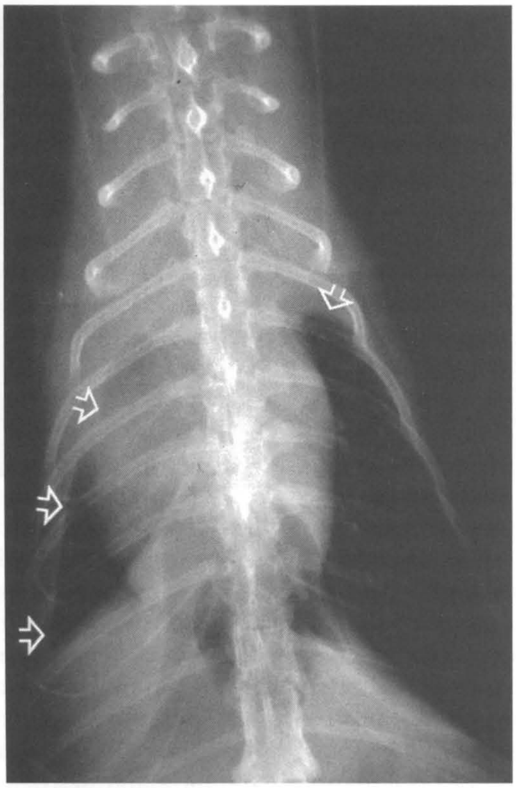


FIGURE 28–19

Ventrodorsal thoracic radiograph of a cat with idiopathic dilated cardiomyopathy and right-sided congestive heart failure. There is generalized moderate cardiomegaly. Pleural effusion causes the lung lobes to retract *(arrows)* and silhouettes the cranial cardiovascular border.

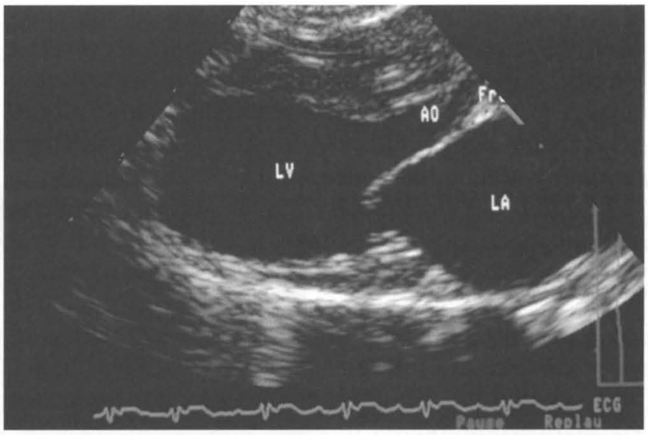


FIGURE 28–20

Two-dimensional echocardiogram (right parasternal long axis view) of a cat with idiopathic dilated cardiomyopathy. There is severe dilation of the left atrium *(LA)* and left ventricle *(LV)*. The LV posterior wall and ventricular septum are thinner than normal. Fractional shortening was markedly reduced (15 percent). *AO*, aortic root.

ECHOCARDIOGRAPHY. Two-dimensional and M-mode echocardiography (and to a lesser extent, Doppler echo) are essential to (1) establish a diagnosis of myocardial failure, (2) assess the degree of cardiac chamber dilation, (3) evaluate the severity of impaired LV contractility, (4) determine the presence and degree of valvular regurgitation, (5) detect diastolic dysfunction, and (6) identify valvular, pericardial, or other diseases. Myocardial failure is present when the fractional shortening is less than 30 percent and the LV end-systolic dimension is greater than 12 mm.

Several patterns of cardiac dilation (Fig. 28–20) and degrees of myocardial failure have been identified. The classic taurine deficiency DCM echo displayed generalized enlargement of all four heart chambers, increased LV and RV end-diastolic and end-systolic dimensions, severely depressed global fractional shortening and ejection fraction, and pericardial and pleural effusion.[4–7, 268, 272]

Current cases of idiopathic myocardial failure[282] generally display either LV dilation with focal segmental LV hypertrophy, or LV dilation with ventricular septal or LV free wall hypokinesis, coupled with hyperdynamic motion of the opposite wall. Biatrial enlargement and variable right-sided enlargement are present. Indices of left ventricular contractility may be mildly to severely compromised, as evidenced by decreased LV ejection time and prolonged pre-ejection period; decreased fractional shortening or circumferential fiber shortening; aortic root, interventricular septal, and

left ventricular free wall hypokinesis; and reduced velocity-time integral. Mild mitral and/or tricuspid insufficiency is commonly detected. Mural LA or LV thrombi may be detected.

ANGIOCARDIOGRAPHY. Echocardiography has largely replaced nonselective angiocardiography for clinical diagnosis. The latter does provide useful information, although with substantial morbidity and mortality and less accuracy compared with diagnostic ultrasound. Salient angiocardiographic features (Fig. 28–21) include generalized chamber dilation, enlarged and tortuous pulmonary veins (and, occasionally, pulmonary arteries), reduced cardiac output suggested by increased circulatory transit time of injected radiocontrast dye, and LA or LV intracavitary thrombi.[5–8, 37, 111]

CLINICAL PATHOLOGY. Laboratory abnormalities are common.[4–7, 34, 36, 37] Most cats are azotemic (e.g., blood urea nitrogen: 35 to 60 mg/dl; normal is 20 to 30 mg/dl), resulting from reduced cardiac output, decreased water consumption, anorexia, and fluid sequestration (effusions). With thromboembolic disease, marked elevations in serum lactic acid dehydrogenase, creatinine phosphokinase, alanine aminotransferase, and aspartate aminotransferase are usually recorded within 24 hours of the embolism. Effusions are usually obstructive transudate or modified transudate.[113]

Normal plasma taurine concentration is greater than 60 nmol/ml; cats at risk measure less than 30 nmol/ml. However, plasma taurine concentration is very labile. Even 24 hours of fasting or anorexia can cause plasma levels to fall below 30 nmol/ml. In contrast, whole blood taurine concentrations are less labile, and fasting does not significantly affect values. Normal whole blood taurine is greater than 200 nmol/ml; cats at risk show less than 100 nmol/ml.[268, 270, 273, 275, 276, 304, 305]

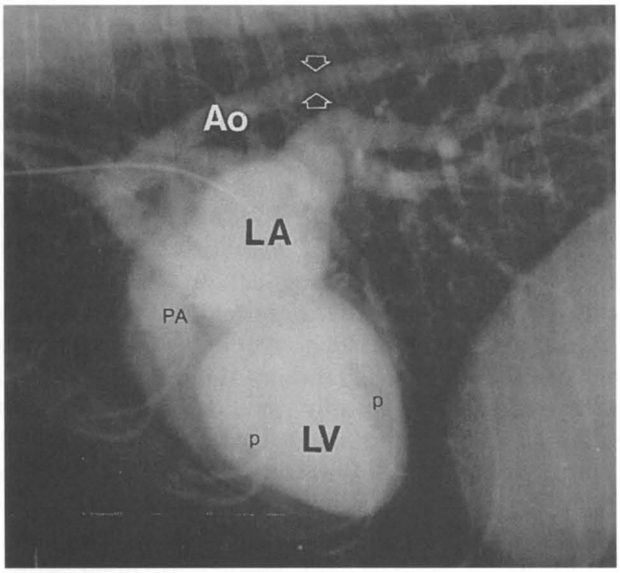


FIGURE 28–21

Nonselective angiocardiogram from a cat with dilated cardiomyopathy. The left atrium *(LA)* is moderately enlarged and the left ventricle *(LV)* is severely dilated. Papillary muscles *(p)* are atrophic. The aorta *(Ao)* is thin and poorly opacified *(arrows)* suggesting diminished forward stroke volume. There is residual radiocontrast dye in the pulmonary artery *(PA)*. (From Fox PR. Feline myocardial diseases. In Fox PR (ed). Textbook of Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 435.)

DIFFERENTIAL DIAGNOSIS

Idiopathic myocardial failure (idiopathic DCM) is diagnosed on the basis of severe LV dilation and impaired contractile performance, after excluding other known etiologic factors. The latter include severe volume overloads caused by mitral regurgitation, aortic regurgitation (rare), and atrioventricular fistulas; left-to-right shunting congenital anomalies; high-output states, such as severe anemia; and taurine deficiency. Because DCM may represent an end-stage condition resulting from a number of etiologies, some cases may display characteristics that overlap other disorders.

Initial Therapy (First 24 to 48 Hours)

TREATMENT GOALS. Initial therapy is directed to reduce or eliminate pulmonary and systemic venous congestion, promote increased forward cardiac output, control serious tachyarrhythmias or bradyarrhythmias, and improve myocardial contractility. General supportive measures, such as external heating to combat hypothermia, oxygen administration, and minimization of undue stress, are important.

THORACOCENTESIS. If breathing is compromised by severe pleural effusion (suggested by muffled heart and lung sounds and a dull note derived by thoracic percussion—or evident by radiography or echocardiography), thoracocentesis is advised. In the severely dyspneic cat, this should be performed even before radiographs are taken. Further diagnostic tests may then be accomplished more safely.

TREATMENT OF ACUTE PULMONARY EDEMA. Life-threatening pulmonary edema is uncommon with myocardial failure (in contrast to the situation with diastolic dysfunction, in which pulmonary edema is the most common sequela of CHF). When edema is severe, furosemide is administered (1 to 2 mg/kg q1–2h IV or IM) to reduce cardiac preload (LV filling pressures) rapidly. The administration frequency is then reduced to the lowest effective level as soon as tachypnea is lessened and thoracic auscultation improves. In some patients cardiac output, albeit decreased, is "sustained" by relatively elevated preload. Overzealous diuresis may severely reduce ventricular filling (preload) and thus drop cardiac output, lead to azotemia and

electrolyte abnormalities and prolong renal clearance of certain drugs (e.g., digoxin).[4–7, 110, 180, 306] Resolution of severe pulmonary edema may be enhanced by administering 2 percent nitroglycerin cream (¼ to ½ inch q8–12h cutaneously) for the first 24 hours. Supplemental oxygen (40 percent to 60 percent oxygen-enriched inspired gas) may be beneficial to improve pulmonary gas exchange.

INTRAVENOUS INOTROPIC SUPPORT. The rationale for positive inotrope administration is based on the presumption of adequate myocardial contractile reserve.[306–311] Synthetic sympathomimetic amines possess greater inotropic activity, provide quicker onset of action, and allow finer control than dose digoxin. They are administered by constant-rate infusion and titrated every 2 to 6 hours to effect to achieve clinical improvement (e.g., stronger femoral arterial pulses, normalization of arterial blood pressure if initially depressed, stronger precordial apex beat, louder heart sounds, reduced lethargy, and improvement of core body temperature). Dobutamine (Dobutrex, Lilly; 2 to 10 μg/kg/min) is the preferred agent for hemodynamic support of the failing heart. It exerts its positive inotropic effects through direct stimulation of myocardial β-adrenergic receptors.[310, 312, 313] At relatively higher infusion rates it increases cardiac output, stroke index, and oxygen transport more effectively than does dopamine.[314] It exerts a lesser effect on the sinoatrial node (and therefore heart rate) than on myocardial tissue and does not stimulate renal dopaminergic receptors.[310, 315–317] However, a common adverse side effect in cats is seizures.[4, 7] These are typically focal facial seizures but occasionally become generalized. Seizures have been observed at infusion rates as low as 5 mg/kg/min. They stop as soon as the dobutamine infusion is discontinued, and often do not recur when the dose is reduced by 50 percent.

If seizures continue at the reduced dosage, dopamine may be substituted. Dopamine is a norepinephrine precursor that preferentially reduces renal vascular resistance and increases glomerular filtration rate, renal blood flow, urine flow, and solute excretion.[318] It directly stimulates cardiac β_1-adrenergic receptors as well as causing release of myocardial stores of norepinephrine.[319] The latter may limit its efficacy if such stores are depleted.[320] At lower doses (< 5 μg/kg/min), hemodynamic effects are relatively small, but it stimulates renal dopaminergic receptors, promoting renal cortical blood flow, glomerular filtration, and diuresis. However, low-dose dopamine infusion may cause ventilatory inhibition in humans and adversely influence outcomes in hypoxic patients with heart failure,[321] although this potential effect has not been studied in cats. Higher doses (> 5 μg/kg/min) stimulate α_1-adrenergic receptors and increase systemic arterial and venous pressures.[322–324] This vasoconstrictor activity is undesirable as it increases impedance to ventricular ejection. Tachycardia, arrhythmias, and increased myocardial oxygen demand may also follow high dosage. Thus, it is a second-line parenteral inotropic agent. Dopamine (Intropin, American Critical Care) is dosed at 2 to 5 mg/kg/min (constant-rate infusion).

TAURINE SUPPLEMENTATION. The only known cause of reversible myocardial failure is taurine deficiency. Because taurine supplementation is effective in such cases,[268] it is empirically administered (250 to 500 mg q12h PO). Analysis of blood taurine concentration ideally should be determined from a blood sample drawn and frozen prior to taurine administration. However, since this assay is not widely available, and because oral taurine supplementation is safe and inexpensive, oral taurine administration is endorsed for any case of myocardial failure.

ANTIARRHYTHMIC MANAGEMENT. Symptomatic or hemodynamically significant tachyarrhythmias are uncommon. For life-threatening ventricular tachycardia lidocaine can be judiciously administered (1-mg boluses administered slowly, up to 1 mg/kg; 15 to 30 μg/kg/min constant rate infusion). Esmolol (Brevibloc, Du Pont Pharmaceuticals, Inc), an ultrashort β-blocker, can be added (50 to 200 μg/kg/min constant-rate infusion) if lidocaine is ineffective, or it can be given for severe supraventricular tachyarrhythmias.

GENERAL SUPPORTIVE MEASURES. In the absence of pulmonary edema, judicious fluid therapy is occasionally beneficial to combat the effect of cardiogenic shock and circulatory failure. Intravenous fluid supplementation may help prevent severe reduction in preload (and cardiac output) and reduces vascular volume contraction caused by diuretics, anorexia, and shock. A mixture of 0.45 percent NaCl (or half-strength lactated Ringer's solution) with 2.5 percent dextrose in water (D_5W) can be given at a submaintenance dose of 20 to 35 ml/kg/day by constant-rate infusion. Potassium chloride must often be supplemented (e.g., 5 to 7 mEq for each 250 ml of fluids). Serum electrolytes should be monitored. The infusion rate and dose vary with each patient and must be balanced to optimize the clinical response without exacerbating pulmonary edema or effusions.[4–7] Central venous pressure monitoring may help guide the infusion rate (chapter 15).

Chronic Maintenance Therapy

A useful approach to maximize chronic therapy for idiopathic myocardial failure emphasizes drug titration to achieve maximum tolerated doses of diuretics, ACE inhibitors, and digoxin as needed. Drug-related toxicity, dehydration, decreased cardiac output (e.g., overzealous preload reduction), and prerenal azotemia are

common management challenges, particularly during the first 7 to 10 days of therapy. The end-points represent simple clinical parameters, such as appetite, activity, body weight, ease (normality) of breathing, heart rate, serum potassium, BUN and creatinine, and development of side effects. Ancillary therapies are dictated by individual needs and may include β-adrenergic blockers, antiplatelet or anticoagulant agents, antiarrhythmics, dietary modification, and detection and treatment of contributory systemic and metabolic diseases (e.g., hyperthyroidism).

DIURETICS. When congestion is controlled, furosemide is tapered to the lowest effective dose. It may be interrupted or temporarily discontinued if azotemia, anorexia, or dehydration occurs. To manage chronic effusions, upward dose titration (1.5 to 4.5 mg/kg q8–12h PO) may be effective in some cats.[4–7, 37] Refractory cases may require periodic thoracocentesis and additional diuretic agents such as hydrochlorothiazide and spironolactone (Aldactazide, Searle; 2.2 to 4.4 mg/kg q24h PO),[113a, 306] although the thiazide may be ineffective in the presence of renal failure.

ACE INHIBITORS. Chronic heart failure causes enhanced RAAS activation, which results in many detrimental effects, including elevated angiotensin II, which contributes to increased preload and afterload and promotes sodium and water retention.[325] ACE inhibitors are thought to act by decreasing angiotensin II production, which in turn improves hemodynamic function. These agents are also used in hopes of limiting progressive cardiac chamber remodeling (dilation) and preventing or delaying clinical deterioration.[326, 327] ACE inhibitor monotherapy has been used to manage successfully some cases of mild idiopathic myocardial failure (fractional shortening, 23 percent to 29 percent; left ventricular end-systolic dimensions, 12 to 14 mm) that have become compensated with diuretics. In more severe cases of systolic failure, ACE inhibitors constitute a component of standard therapy that includes diuretics, and digoxin. Enalapril (0.5 mg/kg PO daily) has a wide clinical safety margin. Many other agents are also available (see Pharmacologic Options and Approaches to Chronic Management, ACE Inhibitors, earlier).

DIGITALIS (DIGOXIN). Although digitalis is the traditional agent for chronic management of myocardial failure, there are few available clinical data concerning cardiomyopathic cats, and digoxin's low therapeutic index makes its role controversial. When digoxin was administered to 6 cats with DCM, small but significant increases in LV systolic function indices were demonstrated in 4 animals; 3 had serum digoxin concentrations in the toxic range.[328] Others have reported no evidence of enhanced survival when digoxin was administered to cats with taurine deficiency DCM.[276] However, clinical benefits of digoxin therapy in the treatment of human heart failure have become evident.[329] Digoxin's efficacy may be related more to its ability to modulate neurohormonal regulation by a direct effect on baroreceptors than to increase cardiac contractility.[330–333]

Digoxin may be administered in pill or elixir form. Although higher plasma levels and more accurate dosing can be achieved with the elixir,[334, 335] it is less palatable to cats than are tablets. The 0.125-mg tablet is readily tolerated, but its small size inhibits accurate division into less than one fourth of a tablet (0.031 mg).[5, 7] Males may develop higher serum levels than females of the same body weight, and food administered in conjunction with digoxin may decrease drug absorption.[334, 335] The biologic half-life of digoxin in healthy cats given a single IV injection is 33.3 ± 9.5 hours. The mean half-life after chronic oral administration of elixir (0.05 mg/kg bid) was 79 hours (range, 33 to 22 hours),[336] indicating that digoxin elimination is capacity-limited in the cat. In DCM cats given oral digoxin in tablet form (0.007 to 0.014 mg/kg q48h), mean half-life was about 64 hours, and steady state was reached after about 10 days.[328] Renal insufficiency will reduce digoxin clearance and increase serum concentration.

Digoxin therapy should be initiated when the cat is hydrated and eating. Initial dosage is guided by body weight and modified by renal function and serum digoxin concentrations. Based upon a calculated dose of 0.005 to 0.01 mg/kg lean body weight and relatively normal BUN/creatinine levels, the following guidelines are suggested:[7] for cats weighing 1.9 to 3.2 kg, ¼ of a 0.125-mg digoxin tablet (0.031 mg) every 2 to 3 days; for cats weighing 3.3 to 6 kg, ¼ tablet daily; and for cats weighing more than 6.0 kg, ¼ tablet daily (occasionally, bid).

Since digoxin is eliminated by renal excretion, dehydration and azotemia may promote digoxin intoxication and warrant dosage reduction, longer interadministration intervals, or drug discontinuation. Serum digoxin concentration should be evaluated 10 to 14 days after initiating therapy. When blood is drawn 10 to 12 hours postadministration, a serum concentration of 1 to 2 ng/ml is presumed to be therapeutic. Toxic plasma concentrations in healthy cats ranged from 2.4 to 2.9 ng/ml.[336] Anorexia and depression are early signs of toxicity.[4–7] Vomiting accompanies more severe intoxication. The most striking ECG changes reported with digoxin toxicosis in one study was ST segment elevation, and P-R interval prolongation may be noted at nontoxic concentrations.[336] Clinical illness in normal cats given toxic doses may last up to 96 hours.[334, 335] In cardiomyopathic cats with reduced cardiac output and renal insufficiency, digoxin toxicity may persist up to 7 days.[4, 5] Concurrent therapy with digoxin tablets (0.01

mg/kg PO q48h), aspirin (80 mg/kg q48h), furosemide (2 mg/kg PO bid) and commercial low-salt diet (h/d, Hills) predisposed normal cats to digoxin toxicity. The precise mechanism of altered digoxin kinetics was not identified.[337]

β-ADRENERGIC BLOCKERS. Because sympathetic nervous system activation in heart failure causes important deleterious effects, β-adrenergic receptor blockade has been advocated for DCM in humans. β-blocker therapy has resulted in improved symptoms, exercise capacity, and LV function in some human DCM patients.[289, 338–343] Potential mechanisms include reduced myocardial oxygen demand due to negative inotropic effect, protection against catecholamine-induced myonecrosis, improved diastolic relaxation, upregulation (increased) myocardial β-adrenergic receptor density, and improved myocardial calcium handling.[342–344] Despite these encouraging findings, clinical benefits of β-blockers have not been evaluated in cats with myocardial failure. When considering their use, one must be mindful of their potential negative chronotropic and inotropic effects in cats with reduced cardiac contractility. It seems rational to judiciously add β-blockers to conventional therapy if myocardial infarction is suspected, or if symptomatic or electrically unstable tachyarrhythmia warrants control of ventricular heart rate. In such cases, a low oral starting dose is recommended (propranolol, 2.5 mg q8–12h or atenolol, ⅛ of a 25-mg tablet q24h). Alternatively, an initial low test dose can be given and patient response observed. Follow-up should include one or more ECGs to assess heart rate and rhythm and echocardiography to evaluate myocardial contractility, cardiac dimensions, and wall motion.

DIETARY MODIFICATIONS. Diet history should be ascertained and adjustments made to eliminate causes of low taurine. Urinary acidification combined with potassium depletion may reduce tissue stores of taurine.[294] Taurine deficiency can also result when inappropriate diets are fed.[263, 268, 295, 296] Oral taurine supplementation should continue if concern exists about dietary deficiency or when taurine depletion is confirmed (plasma taurine less than 30 nm/ml, whole blood taurine less than 100 nmol/ml). Prescription diets for sodium restriction (h/d, Hills) may be considered or home preparation reduced-sodium formulas used in advanced heart failure.

NATURAL HISTORY AND PROGNOSIS

Massive LV dilation is an independent contributor to poor outcome in humans with advanced heart failure, and it may sometimes be stabilized by aggressive drug therapy.[345, 346] In cases of taurine deficiency myocardial failure treated with oral taurine, echocardiographic improvements become noticeable between 3 and 16 weeks after beginning taurine supplementation, but time to recovery is extremely variable. In severely affected cats, mortality is significant within the first 30 days of treatment. Cats surviving more than 1 month remain clinically stable after adequate taurine intake is ensured, and discontinuation of all drugs is usually possible.[268] Echocardiographic improvements include decreased LV end-systolic and end-diastolic dimensions, increased LV wall thickness, and improved LV fractional shortening, although not always to completely normal levels.[268, 272, 275, 276] Cats with idiopathic myocardial failure do not respond to taurine administration. Their clinical course is unpredictable, but symptomatic cats generally have poor prognosis, with a median survival of approximately 13 days.[282] A minority of cats may have a prolonged period of clinical stability, and survival up to 3 years occasionally has been observed. Thromboembolism is a grave complication of cardiomyopathy regardless of cause.

ENDOCARDIAL FIBROELASTOSIS

This rare disease is characterized by diffuse thickening of left ventricular endocardium due to proliferation of fibrous and elastic tissue.[1, 347] There is similarity between the primary form of endocardial fibroelastosis (EFE) reported in humans[347, 348] and that in cats. Endocardial fibroelastosis has chiefly been reported in Siamese[9, 349, 350] and Burmese breeds. A familial pattern of inheritance has been described in Burmese cats.[351–353] Because clinical signs typically develop between 3 weeks and 4 months of age,[35] EFE traditionally has been regarded as a congenital disorder. However, recent evidence supports a hypothesis that human endomyocardial fibroelastosis is a sequela of viral myocarditis, with rapid progression to end-stage.[259]

In cats, a clear separation may not exist between clinical signs exhibited by cats with dilated cardiomyopathy and those of EFE. Reported findings with EFE include dyspnea, systolic murmur of mitral insufficiency, gallop rhythms, tachycardia, hydrothorax, ascites, ECG changes (especially increased R wave voltage), and severe LA and LV enlargement on radiography. At necropsy, the heart weight is increased; there is dilation of the LV and to lesser degree, the LA; and the LV wall is thin. Characteristically, the LV endocardium is diffusely thickened and appears gray-white and opaque.[35] Histologic features are striking and reveal an LV endocardium thickened by dense collagenous and elastic fibers. Therapy has been unrewarding. A secondary variety of EFE, with focal areas of opaque fibroelastic thickening of the mural endocardium, has been reported in association with congenital malformations.[354]

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

DEFINITIONS AND NOMENCLATURE

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by progressive fibrofatty infiltration of the right ventricular myocardium. Initially, this is a regional phenomenon. It progresses to global right ventricular involvement with some left ventricular involvement and relative sparing of the ventricular septum.[3, 355, 356] Classification schemes often overlap or are controversial, and the literature contains a number of confusing terms. Some investigators have used *dysplasia* (i.e., ARVD), a term that implies abnormal tissue growth and differentiation, to describe this disease.[357] However, since this morbid entity is considered a progressive heart muscle disease of unknown etiology, a recent survey by the World Health Organization found a consensus for the term *cardiomyopathy* (i.e., ARVC).[3, 358]

A number of clinical forms of ARVC have been described in humans and are classified under two major subheadings: (1) isolated RV dysplasia (includes the pure form of ARVC, RV outflow tract tachycardia, Uhl's anomaly, nonarrhythmogenic ARVC, and others), and (2) dysplasia with major LV involvement.[359] Arrhythmogenic RV cardiomyopathy characterized by fibrofatty replacement of RV myocardium, with or without changes in wall thickness, should be differentiated from *Uhl's anomaly*, which is distinguished by partial or total absence of RV myocardium. The latter causes marked RV wall thinning because of relative apposition of endocardium and epicardium.[360]

PREVALENCE AND DEMOGRAPHICS

Many cases of ARVC are misdiagnosed as tricuspid valve dysplasia, but recognition of this distinctive cardiomyopathy should increase as its clinicopathologic features become more widely published. The prevalence of ARVC in cats is currently unknown, but it is estimated to represent 2 percent to 4 percent of feline myocardial diseases diagnosed at The Animal Medical Center. Cats from 2 to 20 years of age have been identified with ARVC, and several breeds have been represented.

ETIOLOGY

The polymorphism and wide clinical spectrum of ARVC may be related to consecutive stages of cardiomyopathic disease progression.[361] The majority of humans (80 percent)[361–363] and cats[364] with fibrofatty ARVC have lymphocytic infiltrates within a background of fat interspersed within the myocardium. Thus, it has been speculated that inflammation in early forms of the disease may lead to fibrosis and scarring, thereby transforming the fatty form of ARVC to the fibrofatty form, the latter representing an end-stage of a remote inflammatory process. Alternatively, inflammation may simply constitute a superimposed condition.[365] Recurrent episodes of myocarditis could cause biventricular loss of myocytes, resulting in a pathologic condition similar to end-stage DCM.[365] In addition, an autoimmune response could contribute to myocardial injury and dysfunction.[359] Another potential etiology relates to massive destruction of myocytes through a mechanism of apoptotic myocardial cell death.[364, 367, 368] Lastly, ARVC has a familial occurrence in humans with autosomal dominant inheritance, various penetrance, and polymorphic phenotype expression.[369–372] The possibility that ARVC may be a result of genetic consequences in cats remains to be investigated.

PATHOPHYSIOLOGY

Arrhythmogenic right ventricular cardiomyopathy is a primary heart muscle disorder (cardiomyopathy). It constitutes a dynamic injury-repair process, with a tendency to progress from RV to LV involvement. It is characterized by a progressive loss of myocardium and fibrofatty replacement, which causes cardiac electrical instability. Whether myocarditis is a primary event or occurs secondary to cell death or an autoimmune process is still undetermined.[362] Cell death and fibrofatty replacement constitute a pathologic substrate for arrhythmias, including supraventricular tachyarrhythmias and life-threatening ventricular tachycardia.[373, 374] Severe RV failure results from loss of functional myocytes.

PATHOLOGY

Characteristic gross changes in cats include marked RV and RA chamber enlargement (Figs. 28–22, 28–23). The RV wall thickness may be normal or severely thinned. Thinning may be focally aneurysmal (i.e., external bulging of a thinned ventricular region) or diffuse, and it may facilitate transillumination of light. There is trabecular disarrangement with loss of some trabecular structure, while other trabeculae are fused and distorted, particularly at the RV apex. The tricuspid valve apparatus is distorted owing to severe RV dilation and resultant papillary muscle derangement. Histopathologic lesions are pathognomonic in cats and closely resemble human ARVC lesions. They can be divided into two types: (1) fibrofatty (the predominant form), and (2) fatty myocardial replacement. The fibrofatty form consists of focal or diffuse fibroadipose replacement of myocytes spreading inward from the epicardium, with residual myocytes scattered within fibrofatty tissue. A less common but nevertheless distinctive form is characterized by adipose replacement

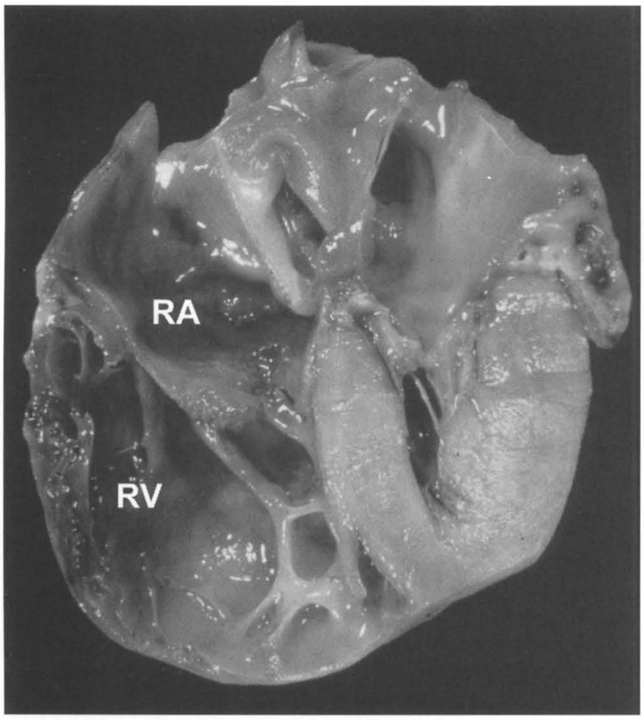


FIGURE 28–22

Gross transverse heart section from a cat with arrhythmogenic right ventricular cardiomyopathy. Characteristic findings include severe dilation of the right atrium (RA) and ventricle (RV), segmental RV wall thinning, and RV trabecular disruption and disorientation.

of myocardium. Myocarditis (inflammatory infiltrates associated with myocyte damage or necrosis) is common, particularly with the fibrofatty variety.

CLINICAL MANIFESTATIONS

HISTORY. The history may be vague and reveal only lethargy, anorexia, or dyspnea. Some cats have syncope due to sustained ventricular tachycardia. Because this condition may develop over a period of time, many cats can be asymptomatic.

PHYSICAL EXAMINATION. Findings may reflect right-sided CHF, including tachypnea, dyspnea, distended abdomen, and jugular venous distention. Thoracic auscultation may reveal muffled heart and lung sounds if pericardial or pleural effusion is present. A holosystolic, regurgitant, soft to medium intensity murmur of

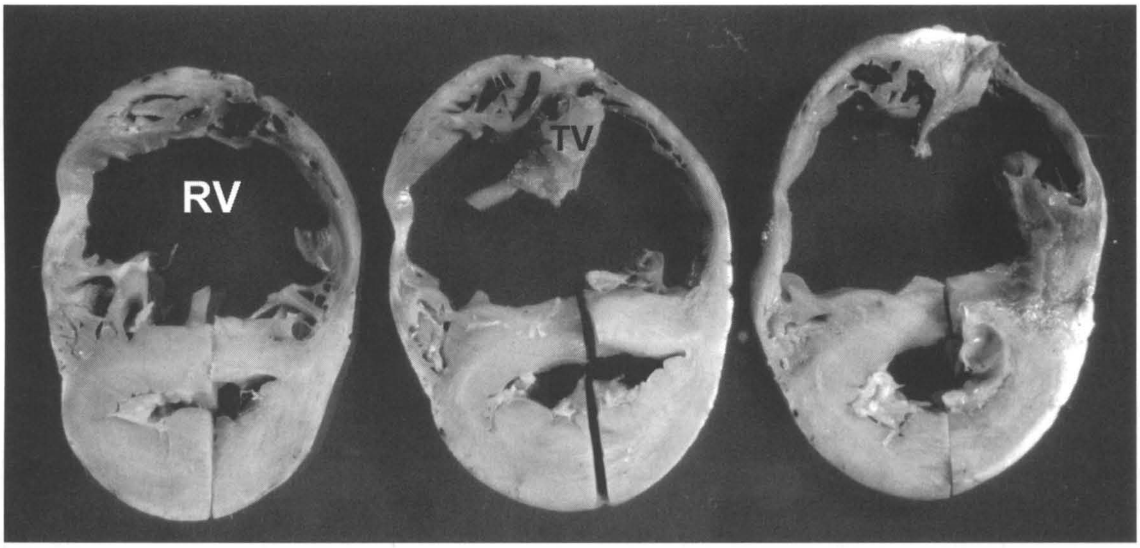


FIGURE 28–23

Gross specimens sectioned sequentially in cross section from a cat with arrhythmogenic right ventricular cardiomyopathy. The right ventricle *(RV)* is severely dilated. *TV,* tricuspid valve.

tricuspid regurgitation is detected in some cats, whereas in others no murmur is present. Femoral arterial pulse deficits are associated with arrhythmias.

ELECTROCARDIOGRAPHY. Abnormalities include supraventricular tachycardias, conduction abnormalities, and ventricular ectopia, frequently with a left bundle branch type of pattern. Some cats may have no recorded changes on short rhythm strips and require Holter monitoring to reveal arrhythmias.

RADIOGRAPHY. Dramatic enlargement of the RA and RV is characteristic. Moderate to severe LA enlargement may also be present. Pleural, pericardial, or abdominal effusions are common.

ECHOCARDIOGRAPHY. Echocardiographic examination discloses severe segmental or diffuse RV dilatation, localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging), severe RA enlargement, abnormal trabecular muscle morphology (especially in the apical RV cavity), and often, LA enlargement with a normal LV or mild LV impairment (Fig. 28–24). Color flow Doppler echo may reveal mild to moderate tricuspid regurgitation. Minor forms of ARVC will have similar but less severe qualitative abnormalities.

DIFFERENTIAL DIAGNOSIS

The most common misdiagnosis is tricuspid dysplasia. Cats with ARVC have striking RV morphologic changes but no valve dysplasia. Tricuspid insufficiency may result from derangement of the tricuspid valve apparatus due to myocardial disease, and the valves are not dysplastic. Right ventricular hypertrophy is not a feature of ARVC. This excludes diseases causing RV dilation with RV hypertrophy (e.g., pulmonary hypertension, right-to-left intracardiac shunts). Biventricular involvement can make diagnosis of ARVC challenging. Pure myocarditis may be arrhythmogenic but would not include characteristic right-sided heart enlargement. Uhl's anomaly must be differentiated by histopathology.

THERAPY

Right-sided CHF is treated with furosemide, digoxin, and an ACE inhibitor. For atrial fibrillation or atrial tachycardia, digoxin combined with diltiazem or atenolol is used to maintain the resting heart rate between 140 and 160 beats/min. Symptomatic ventricular tachycardia has been successfully managed acutely with lidocaine, 15 to 30 μg/kg/min constant rate infusion and chronically with sotalol (2 to 4 mg/kg q12h PO).

NATURAL HISTORY AND PROGNOSIS

This disease appears to progress through several phases in humans: an early "concealed" phase in which sudden death may be the first manifestation; an overt arrhythmic phase; and a final stage of biventricular heart failure resembling dilated cardiomyopathy. Accordingly, this disorder is no longer considered to be limited just to the right side of the heart. The natural history of ARVD is not known in felines, although an arrhythmic phase and a right-sided or biventricular CHF phase has been observed in cats. Treatment of right-sided CHF has been unrewarding, although management of severe ventricular tachyarrhythmias for more than 1 year has been possible.

OTHER MYOCARDIAL DISEASES

INCREASED LV MODERATOR BANDS

A pathologic condition associated with abnormal networks of LV moderator bands has been reported in some cats with cardiomyopathy and heart failure.[4, 5, 7, 22, 266] The significance of these bands and their relationship to the presence of concurrent heart disease is

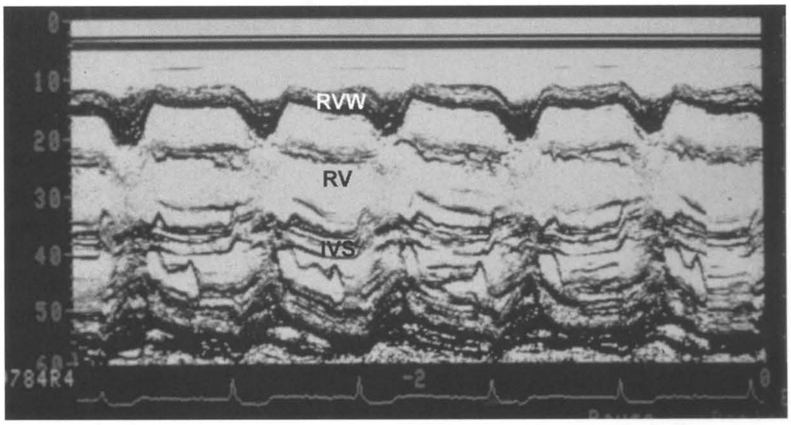


FIGURE 28–24

M-mode echocardiogram recorded at the mitral valve level from a cat with arrhythmogenic right ventricular cardiomyopathy. Notice the severe right ventricular dilation. *RVW*, right ventricular wall; *RV*, right ventricular cavity; *IVS*, interventricular septum.

uncertain because many healthy cats also have networks of LV moderator bands. In a study of 21 cats with increased moderator bands, 11 older cats (mean age, 8.7 years) had dilation of the LV, and 8 younger cats (mean age, 4 years) had LV or septal hypertrophy.[22] Many of the clinical and pathologic findings described were typical of feline DCM or HCM. Mean heart weight in cats with increased moderator bands was less than that in cats with HCM or DCM. Also, conduction disturbances and bradycardia were more common in cats with increased moderator bands compared with cats with other myocardial disorders. It was hypothesized that extensive networks of LV moderator bands (Fig. 28–25) may cause or contribute to cardiac dysfunction in some cats, but that in many instances, they are an incidental congenital anomaly.

UNCLASSIFIED CARDIOMYOPATHIES

Some myocardial diseases have features that do not fit into a discrete category of HCM, RCM, DCM, or ARVC or display characteristics of more than one type of cardiomyopathy. These cases are more appropriately labeled "unclassified cardiomyopathies."[8] Their description can be enhanced by adding a qualifier describing the status of systolic function (i.e., normal versus myocardial failure), as the case may be.

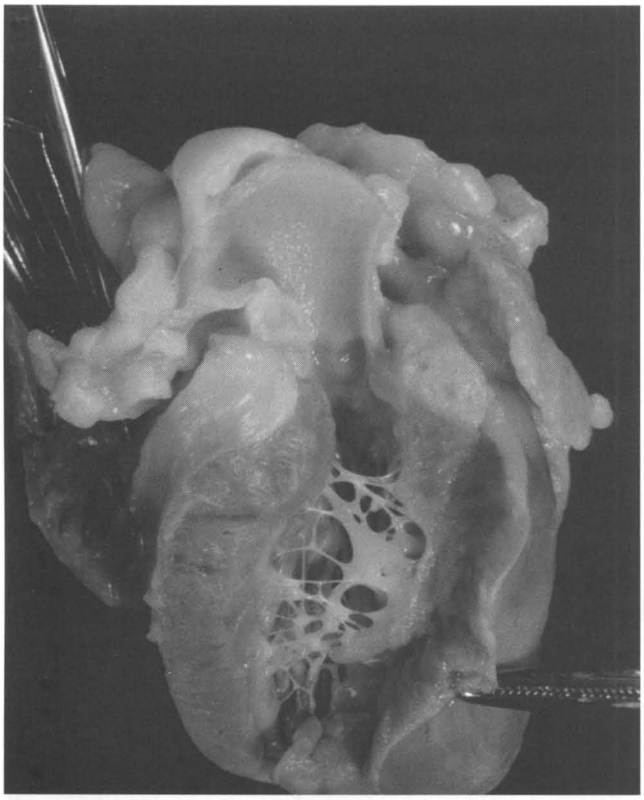


FIGURE 28–25

Heart from an adult cat that died of congestive heart failure. This gross specimen is transected through the left ventricular outflow tract and body of the left ventricle. There is an abnormal network of thickened and excessive moderator bands which bridge the ventricular septum and free wall. The left atrium was moderately enlarged and mild LV hypertrophy was documented by echocardiography.

SECONDARY MYOCARDIAL DISEASES

HYPERTHYROIDISM (CHAPTER 34)

Hyperthyroidism is the most common endocrine disorder of cats. No sex or breed predilections have been identified. Cardiovascular abnormalities are detected in most affected animals, some of which develop arrhythmias and signs of CHF. Early studies reported CHF in as many as 20 percent of affected cats, but the prevalence of this complication appears to have declined with increased awareness and earlier diagnosis.

ACROMEGALY (HYPERSOMATOTROPISM)

A syndrome resembling acromegaly in humans was reported in middle-aged and older cats, with a predisposition for neutered males. These animals had growth hormone–secreting tumors of the pituitary gland.[375, 376] In one study of 14 cats, cardiovascular abnormalities included systolic murmurs (9/14), radiographic evidence of cardiomegaly (12/14), and echocardiographic evidence of septal (7/8) and LV wall (5/8) hypertrophy. None had ECG abnormalities. Blood pressure measurements were not reported. Six cats developed congestive heart failure. Necropsy of 10 cats revealed LV dilation in 1 cat and LV hypertrophy in 7 others. Myocardial histologic lesions included myofiber hypertrophy, multifocal myocytolysis, interstitial fibrosis, and intramural arteriosclerosis.[375] Hypersomatotropism with LV hypertrophy and heart failure has also been identified in a glucose-intolerant, nondiabetic, 12-year-old male cat.[376] One study has reported increased plasma growth hormone concentration in some cats with HCM,[114] although the significance of this finding, and the pathogenesis of heart disease in cats with acromegaly, remain unclear.

SYSTEMIC HYPERTENSION (CHAPTER 35)

The incidence of clinically significant feline systemic hypertension is unknown, although it is an important cause of morbidity in geriatric cats. A variety of sys-

FIGURE 28–26

Transverse gross heart section from a cat with pericardial and pleural effusion, distended jugular veins, and pulmonary edema. Lymphosarcoma had metastasized to occupy both atria (obstructing venous return) and the left ventricular chamber.

temic and metabolic diseases are associated with this condition in cats, especially hyperthyroidism and chronic renal disease, as well as idiopathic arterial hypertension. The pathologic features of feline hypertensive cardiomyopathy have not been described in cats and may be indistinguishable from those described in feline HCM. Suitable therapeutic strategies have now become available for many cases.

MISCELLANEOUS DISORDERS

INFILTRATIVE MYOCARDIAL DISEASE

Neoplastic cardiac infiltration is rare, and most cases involve lymphosarcoma in cats (Fig. 28–26). Diagnosis is usually suspected from radiographs and can sometimes be confirmed by echocardiography. Other cardiac tumors reported in cats include chemodectoma, metastatic hemangiosarcoma, pulmonary carcinoma, and mammary gland carcinoma.[4–7, 262a, 377, 377a] Reported cardiac abnormalities include arrhythmias and pericardial and pleural effusion. Regression of neoplastic infiltration was observed in one cat with lymphoma following treatment with combination chemotherapy.[262a]

DRUGS, TOXINS, AND PHYSICAL INJURY

Many agents can injure the heart, but very few are identified in feline practice. Doxorubicin has received the most attention.[378–380] Decreased fractional shortening and increased LV end-systolic dimensions were recorded in 4 of 6 experimental cats given cumulative doses of 170 to 240 mg/m.[380] However, neither heart failure nor ECG abnormalities were observed. Pathologic changes were evident, including extensive myocyte vacuolization and myocytolysis. Similar clinical observations have been reported in cats with malignancies treated with doxorubicin. None developed overt heart failure, and arrhythmias were only rarely observed.[378, 379] Heat stroke and blunt trauma (e.g., "high-rise" syndrome) are the most common physical causes of myocardial injury.

MYOCARDITIS

Although myocarditis is infrequently recognized, it may play an important role in certain myocardial diseases (see earlier etiology discussions for RCM, DCM, and ARVC).[141, 242, 244, 256–262, 276, 359–366, 381, 382] A syndrome of acute, nonsuppurative myocarditis and acute, unexpected death was described in 25 young cats (mean age, 2.6 years).[381] Pathologic lesions included diffuse or focal endomyocardial infiltration with mononuclear cells and occasional neutrophils. Etiology was not identified. Other reported causes of myocarditis in cats include toxoplasmosis[383] and metastatic infection from sepsis or bacterial endocarditis (Fig. 28–27).[4–7, 35, 37, 384, 385]

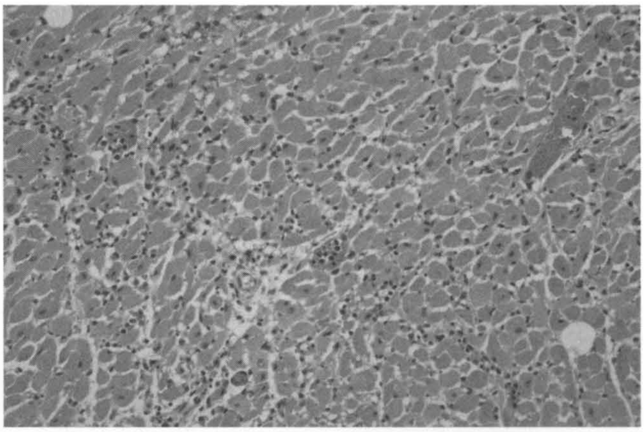


FIGURE 28–27

Photomicrograph of a left ventricular section from a cat with suppurative myocarditis. There is a diffuse, moderate inflammatory infiltrate comprised predominantly of neutrophils. (Hematoxylin and eosin stain, 100×.)

PERSISTENT ATRIAL STANDSTILL AND OTHER UNCOMMON DISORDERS

Persistent atrial standstill has been reported in 11 cats (8 Siamese, one Burmese, two mixed-breed cats).[266, 386] Seven cats were necropsied, and all had DCM with severe atrial myocardial atrophy. In contrast to dogs with atrial standstill, none of the cats had evidence of skeletal muscular dystrophy. In this series, persistent atrial standstill appeared to be an uncommon sequela of chronic DCM. Cardiac involvement has been described in several cats with a Duchenne-like muscular dystrophy.[387] Genetic mucopolysaccharidosis has been reported in cats—Hurler's syndrome (MPS I) in domestic shorthair cats[388] and Maroteaux-Lamy syndrome (MPS VI) in Siamese cats,[389] but cardiac involvement has not been significant. Conduction system lesions may occur in cats with cardiomyopathy. Bundle branch fibrosis, infiltration, and degeneration and AV node degeneration have been reported.[9, 390]

ARTERIAL THROMBOEMBOLISM

DEFINITIONS AND NOMENCLATURE

Thrombotic and thromboembolic complications of feline cardiomyopathy have long been recognized.[391] *Thrombosis* represents clot formation within a cardiac chamber or vascular lumen. Thrombi can be located in the left atrial cavity (often referred to as "ball" thrombus), left ventricular cavity, or both. Within the LA, thrombus may be found in the body of the LA, in the atrial appendage, or in a combination of these areas. *Embolization* occurs when a clot or other foreign material lodges within a vessel.[392, 393] The systemic arterial system is almost exclusively involved, as right-sided heart and deep venous thrombosis are rare in cats.

PREVALENCE AND DEMOGRAPHICS

Cardiogenic emboli frequently complicate the course of myocardial disease and result in significant morbidity and mortality.[4–7, 9, 21, 22, 24, 25, 33–37, 69, 99, 394–396] At necropsy, thromboembolism has been reported in up to 48 percent of HCM cats,[24, 396–398] 29 percent of RCM,[9] 25 percent of DCM,[24, 398] and 14 percent of cats with excessive LV moderator bands.[22] The prevalence in the general population is undoubtedly less than that detected from necropsy surveys. Clinical studies have reported incidences of arterial thromboembolism ranging from 16 percent to 18 percent in taurine deficiency DCM;[272, 276] 18 percent in idiopathic myocardial failure;[262] 12 percent in HCM;[33] 13 percent of cats with nondilated LV hypertrophy;[101] and 19 percent of 46 HCM cats either at clinical presentation or during long-term follow-up.[25] Most cats with systemic arterial thromboembolism have CHF concurrently at the time of clinical embolism.[4–7, 25] Thromboembolism is uncommon with hyperthyroidism, and a 3 percent incidence of thyrotoxicosis was recorded in 100 cats with saddle embolism.[396]

Age of occurrence for thromboembolism ranged from 1 to 20 years (mean, 7.7 years; median, 10.5 years) in one report. The highest incidence occurred in 4- and 7-year-old cats. A male preponderance was recorded (67 percent); 63 percent were neutered. Ninety-one percent were domestic varieties.[396]

The site of cardiogenic embolism is variable, but distal aortic ("saddle") embolization is the predominant clinical location in more than 90 percent of cats affected with thromboembolic complications (Fig. 28–28). The right brachial artery is occasionally occluded (the left brachial artery is only rarely embolized). Left-sided heart mural thrombi are sometimes present (see Figs. 28–14, 28–15), particularly in the left auricle and less often in the left ventricle. Various other organs may become embolized as a consequence of systemic embolic "showers," especially the kidneys and, less often, the mesenteric arteries.

PATHOPHYSIOLOGY

Pathogenesis of thrombosis requires one or more of three essential conditions to be present:[399–401] (1) local vessel or tissue injury, (2) circulatory stasis, and (3) altered blood coagulability. Known as *Virchow's triad,*[402] these prothrombotic factors are invariably present to some degree in myocardial diseases that make cardiomyopathic cats predisposed to thromboembolic events.

LOCAL TISSUE INJURY. Endomyocardial injury is common in all forms of feline cardiomyopathy.[9, 21, 24–26, 36,

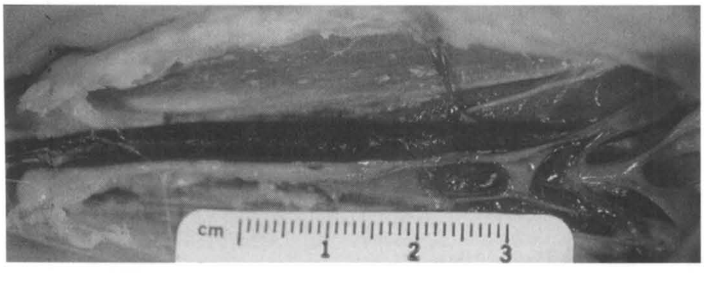


FIGURE 28–28

Dissection exposing the distal aorta of cat with restrictive cardiomyopathy that died from heart failure. There is an occlusive saddle embolism at the aortic trifurcation. The distal posterior vena cava is just above the aorta.

[99, 104, 266, 392] Myocardial infarction, endomyocarditis, or aneurysms may occur. More commonly, endothelial fibrosis may be present in the left atrium, left ventricle, or both. Areas of fibrosis may be patchy, focal, or diffuse and are composed of hyaline, fibrous, and granulation tissue with collagenous fibers. Such lesions may present reactive substrates to circulating blood and trigger a thrombotic process by inducing platelet adhesion and aggregation, with subsequent activation of the intrinsic clotting cascade. In addition to fibrillar collagen, exposed thromboplastin or tissue factors may contribute to thrombogenicity.[403, 404]

STASIS. Blood stasis predisposes to thrombosis.[163, 164, 170, 405] Cardiac chamber dilation, particularly when associated with reduced contractility, results in large end-systolic volumes and blood stasis.[393, 406] Thrombi are most frequently found in the left atrial appendage in cats regardless of the type of cardiomyopathy, presumably the consequence of poor atrial emptying. Impaired blood flow decreases clearance of activated clotting factors, which sets up clot formation in areas of tissue injury.

HYPERCOAGULABLE STATES. A hypercoagulable environment may be present in some cardiomyopathic cats with thromboembolism. Disseminated intravascular coagulation associated with consumptive coagulopathy, liver-mediated coagulopathy, or thromboembolism was present in more than 75 percent of affected cats.[407, 408] In addition, feline platelets are very reactive and responsive to adenosine diphosphate (ADP) and other agonists of platelet aggregation.[409, 410] Serotonin, a vasoactive amine, is released from platelets where it is present in high concentrations in cats and further enhances platelet activation.[411] Others have reported that platelets from cats with cardiomyopathy had increased responsiveness (aggregation) to collagen but decreased responsiveness to ADP.[412] Recently, the influence of hypercoagulable states in human thrombogenesis has become the focus of great interest, and a large menu of tests has emerged to evaluate these disorders. The hypercoagulable states most commonly evaluated in humans at this time include resistance to factor V Leiden (APC), proteins C and S deficiency, antithrombin III (AT III) deficiency, antiphospholipid syndrome, and hyperhomocysteinemia.[413] In a study of 11 cats with cardiomyopathy (7 due to hyperthyroidism), mean AT III activity was increased and AT III behaved as an acute-phase reactant.[412] It is interesting that hyperhomocysteinemia is present in some cardiomyopathic cats with thrombosis (Hohenhaus AE, Simantov R, Fox PR, unpublished data, 1998). These and related conditions must be more fully evaluated in cats with systemic thromboembolism and may play a significant role in their management and prevention.

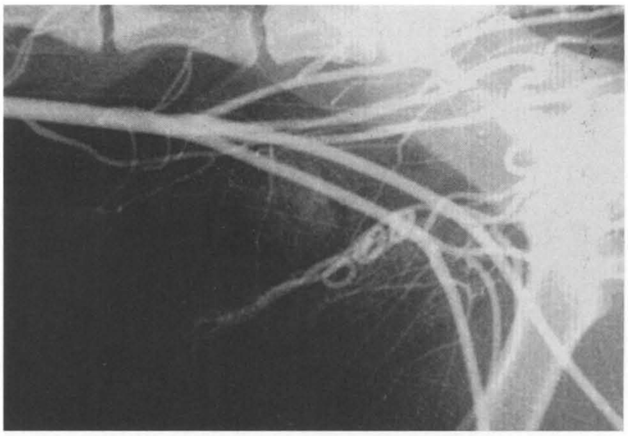


FIGURE 28–29

Distal aortic angiogram from a healthy cat illustrates the normal vascular anatomy in the region of the aortic trifurcation.

ROLE OF COLLATERAL CIRCULATION. Collateral circulation plays a critical role in progression and resolution of clinical thromboembolic disease (Fig. 28–29), and it is modulated by vasoactive substances (e.g., serotonin and others) released by the clot and other substrates.[414, 415] For example, simple distal aortic ligation does not duplicate the clinical syndrome caused by a saddle embolus, whereas experimentally induced aortic thromboembolism simulates the naturally occurring syndrome.[416, 417] Chemicals such as thromboxane A_2 also cause vasoconstriction[418] whose synthesis can be reduced by antiprostaglandin drugs such as aspirin.[419]

PATHOLOGIC CONSEQUENCES OF OCCLUSIVE ISCHEMIA. The functional integrity of an extremity depends to a large extent on adequate arterial blood supply. Sudden arterial occlusion with almost instantaneous and complete interruption, coupled with decreased collateral circulation, causes substantial tissue injury. Ischemic neuromyopathy is a predictable consequence of arterial occlusion and, in particular, of clot associated with inhibition of collateral circulation (Fig. 28–30).[420] Ischemia abolishes rapid axoplasmic neuronal flow causing conduction failure, which becomes irreversible after 5 or 6 hours. Distal aortic (saddle) embolization causes peripheral nerve lesions, starting at the midthigh region. The majority of nerve fibers display a wallerian-type of degeneration while some exhibit damage to the myelin sheath only. Clinically, the duration of peripheral nerve function can induce pathologic neuromuscular changes. Focal necrosis, myophagia, and architectural changes may be evident histologically.[420] Distal limbs below the stifle are most severely injured. Cranial tibial muscles are more affected than gastrocnemius muscles, inhibiting hock flexion more than extension. Hip flexion and extension are maintained. The result is a dragging motion of the hind legs. Distal limb sensation is severely affected.[416]

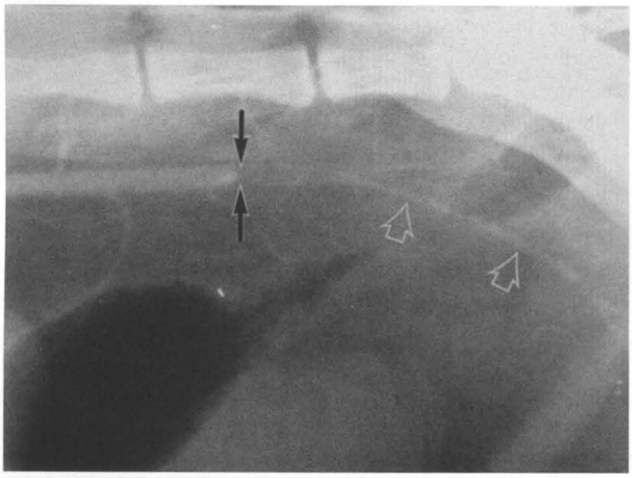


FIGURE 28–30

Distal aortic angiogram of a cat with hypertrophic cardiomyopathy taken two days after it developed acute posterior paresis. The aortic dye is abruptly interrupted *(black arrows)* by a saddle embolism located at the aortic trifurcation. A small column of contrast dye *(open arrows)* appears distal to the block and indicates partial recanalization. However, there is no significant collateral circulation.

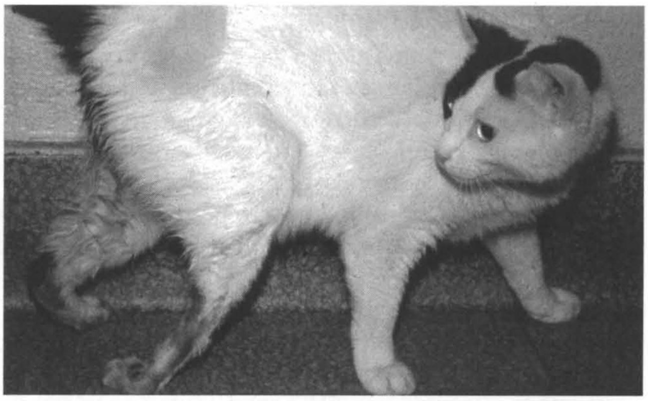


FIGURE 28–31

Cat with restrictive cardiomyopathy and lateralizing posterior paresis caused by a distal aortic (saddle) embolism. This animal originally presented with bilateral posterior paresis. It gradually regained motor ability of its left rear leg, which became weight bearing at the time of this photograph taken two weeks after initial presentation. However, an additional three weeks was required for the cat to support weight on its right rear leg.

CLINICAL MANIFESTATIONS

The clinical consequences of arterial thromboembolism depend upon (1) the site of embolization, (2) the severity and duration of occlusion, (3) the degree of functional collateral circulation, and (4) development of serious complications (e.g., hyperkalemia, limb necrosis, self-mutilation). If thromboembolism is suspected, a minimum data base should be generated to include thoracic radiographs, ECG, echocardiogram, biochemical profile, urinalysis, and feline leukemia virus/feline immunodeficiency (FeLV/FIV) test.

HISTORY. Distal arterial embolism characteristically results in peracute clinical signs of lateralizing paresis, vocalization, and pain. Occasionally, intermittent claudication or right front paresis is reported. Signs of CHF are often present concurrently, including dyspnea, tachypnea, anorexia, and syncope.

PHYSICAL EXAMINATION. Clinical signs are attributable to CHF and specific tissues or organs that are embolized (e.g., azotemia from renal infarction, bloody diarrhea from mesenteric infarction, posterior paresis from saddle embolus). More than 90 percent of affected cats present with a lateralizing posterior paresis caused by a "saddle clot" at the distal aortic trifurcation (Fig. 28–31). Clinical signs are characterized by the four Ps that relate to the extremities: *Paralysis, Pain, Pulselesness* (lack of palpable femoral arterial pulses), and *Polar* (cold distal limbs and pads). Cranial tibial and gastrocnemius muscles are often firm or become so from ischemic myopathy by 10 to 12 hours postembolization. In most cases they become softer 24 to 72 hours later. Acutely affected cats can move their back legs by virtue of flexing and extending the hip in a "dragging" manner, but they cannot flex and extend the hock. Invariably, one leg is more severely affected than the other. Nail beds are cyanotic, and distal limbs are commonly swollen. Occasionally, a single brachial artery is embolized, causing monoparesis (usually the right front leg) (Fig. 28–32). Intermittent claudication may be observed. In such cases arterial pulses may be palpated, foot pads feel warm (normal), and nail beds are not cyanotic. This frequently precedes a more severe thromboembolic event. Less common sites of em-

FIGURE 28–32

Cat with hypertrophic cardiomyopathy and acute right front leg paresis caused by brachial artery embolization.

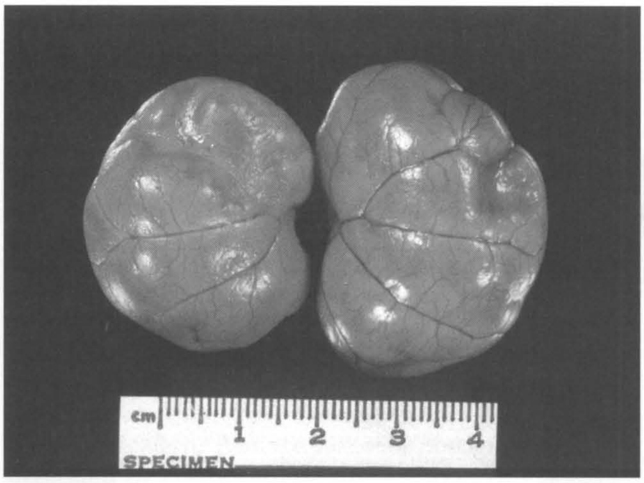


FIGURE 28–33

Kidneys from a cat managed for chronic heart failure, cardiomyopathy, and thromboembolism. Renal surfaces contain irregular sunken regions caused by chronic infarction.

bolization include renal, mesenteric, pulmonary, coronary, and cerebral arteries (Figs. 28–33, 28–34, 28–35). Occlusion of these sites may cause rapidly progressive deterioration and death. Abnormalities detected during thoracic auscultation are common, including heart murmurs, gallop rhythms, pulmonary crackles, or muffled heart and lung sounds. Most affected cats are clinically dehydrated, and many are hypothermic.

THORACIC RADIOGRAPHY. Cardiomegaly is usually evident. In most cases biatrial enlargement is present, and the left auricular appendage is often prominent in the ventrodorsal or dorsoventral view. The majority of affected cats have concurrent extracardiac signs of congestive heart failure (e.g., pulmonary edema, pleural effusion).[4–7, 25, 396] Normal cardiac silhouettes were reported in 11 percent of cats with thromboembolism.[396]

ELECTROCARDIOGRAPHY. In one large retrospective study of cats presenting for thromboembolism, 85 percent had ECG changes whereas only 15 percent had no ECG abnormalities. Sinus rhythm was present in 60 percent. Seven percent had supraventricular tachycardia, including atrial fibrillation; 3 percent had ventricular tachycardia; and 28 percent had sinus tachycardia. Isolated supraventricular (19 percent) and ventricular extrasystoles (19 percent) were also recorded.[396] As underscored by continuous ECG (Holter) recordings in cats with CHF and systemic thromboembolism, important changes can occur in heart rate and rhythm. Development of atrial standstill and a sinoventricular rhythm indicates hyperkalemia, a catastrophic consequence of reperfusion muscle injury.[115]

CLINICAL PATHOLOGY. Most cats have clinical pathology abnormalities.[396, 407, 408] Elevated BUN and creatinine levels were recorded in a little over half of cats at presentation.[396] Mild prerenal azotemia is common since many cats are dehydrated, although renal infarction may play a role in some cases.[4, 5, 8, 266, 407] Serum concentrations of alanine aminotransferase (SGPT) and aspartate aminotransferase (SGOT) are elevated by about 12 hours and peak by 36 hours postembolization, indicating hepatic and skeletal muscle inflammation and necrosis. Lactate dehydrogenase (LDH) and creatine phosphokinase (CPK) enzymes are greatly increased shortly after embolization, indicating widespread cellular injury. Hyperglycemia, mature leukocytosis, lymphopenia, and hypocalcemia may be present. Acute hyperkalemia can result from reperfusion injury of skeletal muscles downstream from the embolus. Hypokalemia is a common consequence of anorexia and diuretic therapy.[5, 7, 113a] Coagulation abnormalities may be detected.[408] Some affected cats have hyperhomocysteinemia (Hohenhaus AE, Simantov R, Fox PR, unpublished data, 1998).

ECHOCARDIOGRAPHY. Echocardiography provides rapid, noninvasive assessment of cardiac structure and function, detects intracardiac thrombi when present, and thereby assists in formulating appropriate therapy and prognosis. Multiple imaging planes are required to detect small mural thrombi, particularly in the left auricular appendage. *Spontaneous echo contrast* ("smoke") may be present in the LA or LV. It is associated with blood stasis and is considered a harbinger and marker for increased thromboembolic risk[162–164] (see Fig. 28–14). The mechanism of smoke has been attributed to erythrocyte aggregation at a low shear rate[165, 166] or platelet aggregates.[167, 168] (See Spontaneous Echo Contrast ["Smoke"] and Stasis, under Hypertrophic Cardiomyopathy, earlier.) Left atrial enlargement (LAE) is usually but not invariably present. In a retrospective study of cats with saddle emboli, severe LAE (LA:Ao ratio $\geq$ 2.0) was recorded in 57 percent, moderate LAE (LA:Ao 1.63 to 1.99) in 14 percent, mild LAE (LA:Ao, 1.25 to 1.629) in 22 percent, and 5 percent of cats had normal LA measurements (LA:Ao $<$ 1.25).[396]

ANGIOCARDIOGRAPHY. Nonselective angiocardiography can be considered in the stabilized patient if echocardiography is not available. In this scenario, it can help determine the type of cardiomyopathy and disclose the presence of LA or LV ball thrombi, if any. It is occasionally used to determine the anatomic location or extent of systemic thromboembolism and to assess collateral flow (see Figs. 28–29, 28–30, 28–34, 28–35). The technique is relatively simple and requires sedation, jugular venipuncture with a large-gauge (e.g., 19-gauge) needle, hand injection of radiocontrast dye (0.8 to 1.8 mg/kg IV), and rapid, sequential exposure of radiographic cassettes.[111] This technique is not with-

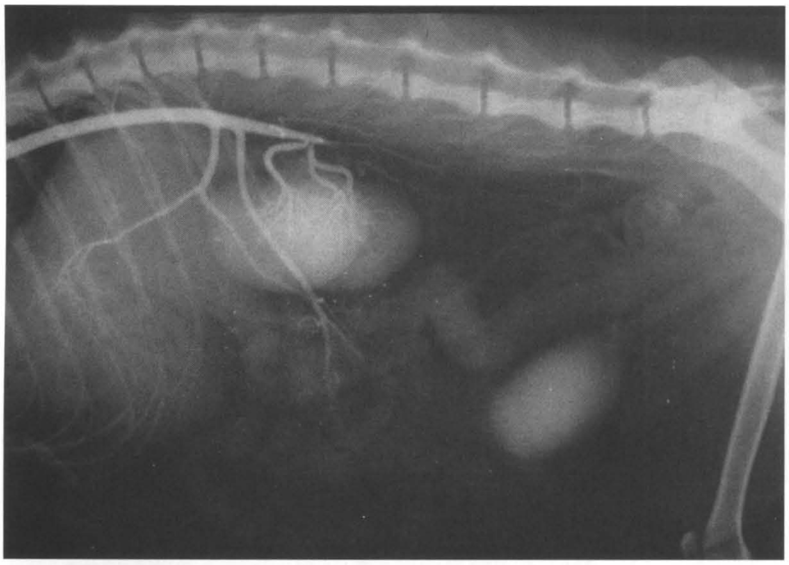


FIGURE 28–34

Aortic angiogram from a cat with thromboembolic complications of cardiomyopathy. The dye is blocked just past the renal arteries, indicating a massive embolism distal to this location.

out risk in decompensated animals. Severe myocardial failure and hemodynamically or electrically unstable arrhythmias constitute relative contraindications.

DIFFERENTIAL DIAGNOSES

Differential causes of acute posterior paresis include trauma, intervertebral disc extrusion, spinal lymphosarcoma and other neoplasia, and fibrocartilaginous infarction. Acute front leg monoparesis can be caused by trauma, foreign body, and brachial plexus avulsion. The diagnosis is relatively easy to confirm by physical examination (gallop rhythm; murmur; arrhythmias; cold, pulseless limbs), radiographic and echocardiographic evidence of cardiomegaly and often heart failure, and clinical pathology abnormalities. Thromboembolism uncommonly occurs in the setting of a structurally normal or mildly abnormal heart. Neoplasia is sometimes discovered in the thorax or abdomen (although the mechanistic relationship, if any, is unclear), or systemic inflammation or endocarditis can represent cardiovascular sources of emboli.

NATURAL HISTORY AND PROGNOSIS

Short-term prognosis depends on the nature and responsiveness of the cardiomyopathic disorder and heart failure state. In cases of saddle embolism, motor ability may begin to return in one or both legs within 10 to 14 days (see Fig. 28–31). By 3 weeks, significant motor function (i.e., hock extension and flexion) has often returned, typically better in one leg than in the other. Motor function may be completely normal by 4 to 6 weeks, although a conscious proprioceptive deficit or conformational abnormality (e.g., extreme hock flexion) may persist in one leg. Unfortunately, most

FIGURE 28–35

Nonselective angiocardiogram from a cat with hypertrophic cardiomyopathy with congestive heart failure, posterior paresis, and bloody diarrhea. The aorta is occluded by a massive embolism after it enters the abdomen. The diarrhea was associated with ischemic bowel necrosis. Notice the gas-filled loops of bowel. The cat experienced acute renal failure and hyperkalemia and died.

cats experience additional thromboembolic episodes within days to months of the initial event, although survivals of several years, including repeat embolic episodes, have been observed.[4, 5, 7, 407] In one large retrospective study, 34 of 92 cats (37 percent) survived an initial event of saddle embolism. Follow-up information was available for 22 of these 34 cats, and an average long-term survival of 11.5 months was recorded.[396]

CLINICAL INDICATORS OF A RELATIVELY FAVORABLE PROGNOSIS. Thromboembolism is a well-established cause of morbidity and mortality and represents a severe clinical complication. A more favorable prognosis may be suggested by (1) resolution of CHF and/or control of serious arrhythmias, (2) lack of LA/LV thrombi or spontaneous echo contrast, (3) re-establishment of appetite, (4) maintenance of relatively normal BUN/creatinine and electrolyte levels, (5) return of limb viability and function (e.g., loss of swelling, return of normal limb temperature, return of motor ability), (6) return of femoral arterial pulses and pink nail beds, (7) lack of self-mutilation, and (8) committed owner.

CLINICAL INDICATORS OF GRAVE PROGNOSIS. A number of morbid events confer a grave prognosis: (1) refractory CHF or development of malignant arrhythmias, (2) acute hyperkalemia (from reperfusion of injured muscles), (3) declining limb viability (e.g., progressive hardening of the gastrocnemius and anterior tibial muscle group (Fig. 28–36); failure of these muscles to become soft 48 to 72 hours after presentation; development of distal limb necrosis), (4) clinical evidence of multiorgan or multisystemic embolization (e.g., neurologic signs, bloody diarrhea, acute renal failure) which usually accompanies extensive thromboembolism (see Figs. 28–34, 28–35), (5) history of previous embolic episodes, (6) presence or development of LA/LV thrombus or spontaneous echo contrast, (7) rising BUN/creatinine levels, (8) disseminated intravascular coagulation, (9) unresponsive hypothermia, (10) severe LA enlargement with arrhythmia and myocardial failure, and (11) uncommitted owner with limited financial resources.

Therapy of Thromboembolism

TREATMENT GOALS

Therapy is directed toward (1) managing concomitant CHF or serious arrhythmias when present, (2) general patient support, including nutritional supplementation, correction of hypothermia, and prevention of self-mutilation, (3) adjunctive therapies to limit thrombus growth or formation, (4) close patient monitoring for limb viability, heart rate and rhythm, progression or regression of CHF, BUN/creatinine and electrolyte levels and appetite, and (5) prevention of repeated events.

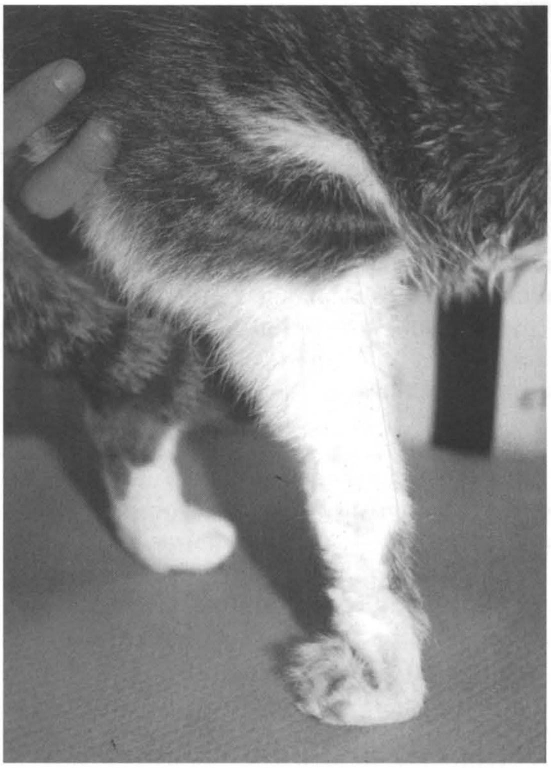


FIGURE 28–36

This cat with hypertrophic cardiomyopathy, congestive heart failure, and a saddle embolism developed severe atrophy of the right rear gastrocnemius and cranial tibial muscle groups. In this photograph the head is oriented to the right, the left rear leg is in the background, and the right rear leg is in the foreground. By four weeks post embolization, this resulted in permanent flexure contracture of the metatarsal-phalangeal joint while the other leg regained normal function. Despite these changes, the cat could walk on the dorsal aspect of its right proximal phalanges and tolerated a small, soft padded foot bandage, which the owner changed frequently. The pet maintained an indoor-outdoor life style and survived 14 months until it experienced a second embolism.

THROMBOLECTOMY

Acutely affected cats are a high surgical/anesthesia risk due to CHF, hypothermia, disseminated intravascular coagulation, and arrhythmias.[4–7, 9, 35–37, 395, 398, 406, 421] Thus, acute embolectomy or surgery is generally contraindicated. Results have been poor, and these procedures have fallen into disfavor.

VASODILATOR THERAPY

Various medical treatments have been proposed, although most are empirical and efficacy is unsubstantiated. The use of acepromazine maleate or hydralazine to encourage arterial vasodilation has been suggested.[35, 396] However, arterial dilation may not be uniform, and flow to muscle beds may not be altered.[422] Moreover, these agents are potentially hypotensive,

and they have not been shown to alter platelet-induced reduction of collateral flow caused by vasoactive chemicals such as serotonin.

THROMBOLYTIC THERAPY

RATIONALE. Limb and/or organ viability is enhanced by rapid resolution of arterial occlusion. Platelets constitute a large component of occlusive arterial emboli. In addition, activated platelets provide a catalytic surface for activation of prothrombin and factor X and may therefore contribute to thrombus initiation, growth, and extension.[423, 424]

STREPTOKINASE. Streptokinase and urokinase act by generating the nonspecific proteolytic enzyme plasmin through conversion of the proenzyme plasminogen. This causes a generalized lytic state, with the incipient hazard of bleeding complications.[425] Streptokinase was studied in a feline model of experimentally induced aortic embolism.[426] It was administered as an IV loading dose (90,000 IU/cat over 20 to 30 minutes), followed by a constant-rate infusion (45,000 IU/h) for 3 hours. With this approach, streptokinase predictably produced systemic fibrinolysis with no detectable adverse effects, but it failed to produce significant improvement as measured by venous angiograms, thermal circulatory indexes, or statistically significant reduction in mean thrombus weight. However, a studied clinical evaluation of streptokinase in naturally occurring feline thromboembolism and cardiomyopathy has not been reported.

RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR. Tissue plasminogen activator (t-PA) has a lower affinity for circulating plasminogen and does not induce a systemic fibrinolytic state. It binds to fibrin within the thrombus and converts the entrapped plasminogen to plasmin. This initiates a local fibrinolysis with limited systemic proteolysis.[427] Tissue plasminogen (Activase, Genentech) was evaluated in cats with spontaneous thromboembolism.[428] It was administered IV at a rate of 0.25 to 1.0 mg/kg/hr for a total IV dose of 1 to 10 mg/kg. Successful thrombolysis, defined as evidence of reperfusion within 36 hours of t-PA administration, was reported in 50 percent of the thromboembolic cats; 43 percent of the cats survived therapy and ambulated within 48 hours of presentation. However, 50 percent of the cats died during therapy, which raised major concerns regarding rapid thrombolysis. Complications resulted from hyperkalemia due to reperfusion syndrome (70 percent), heart failure (15 percent), or sudden death (15 percent). Bleeding into and around the kidney was also observed in several cats. Widespread clinical interest in this agent has been inhibited by its high cost.

ANTICOAGULATION THERAPY

RATIONALE. Anticoagulants (heparin, coumarin) have no effects on established thrombi. Their use has been based on the premise that by retarding clotting factor synthesis or accelerating its inactivation, thrombosis from activated blood-clotting pathways can be prevented. In cats who have suffered previous thromboembolism, or in patients with a predisposition for thrombosis, oral anticoagulant therapy may offer a decreased risk of thromboembolism in exchange for an increased risk of major hemorrhage. It should not be attempted without vigilant monitoring and appropriate patient selection.

HEPARIN. Heparin (heparin sodium, Liquaemin) binds to lysine sites on plasma antithrombin III, enhancing its ability to neutralize thrombin and activated factors XII, XI, X, and IX; this prevents activation of the coagulation process.[429] The efficacy of heparin therapy has been established in many human trials and in experimental animal models for prevention and treatment of venous and pulmonary arterial thrombosis.[430] Efficacy in treating cats with spontaneously occurring thromboembolism has never been established, and its use for this indication remains controversial. Reported dosages vary widely. It may be administered at the time of admission as an initial IV dose (100 to 200 IU/kg), then 50 to 100 IU/kg subcutaneously q6–8h.[396] The dose is then adjusted to prolong activated partial thromboplastin time (APPT) one and a half to two times pretreatment values. Bleeding is a major complication. Clotting profiles must be closely monitored.

COUMARIN. The coumarin drug warfarin (Coumadin Tablets, DuPont) impairs hepatic vitamin K metabolism, a vitamin necessary for synthesis of procoagulants (factors II [prothrombin], VII, IX, and X).[431] The initial oral daily dosage (0.25 to 0.5 mg/cat) is adjusted to prolong the prothrombin time (PT) to twice the normal value; alternatively, it is adjusted by the international normalization ratio (INR) to maintain a value of 2.0 to 3.0, as follows:

$$\text{INR} = [\text{Cat prothrombin time} \div \text{Control prothrombin time}]^{\text{ISI}}$$

By this monitoring technique, evaluation of anticoagulant therapy with the PT is adjusted for variations in thromboplastin reagent and laboratory technique. The laboratory should provide an index of sensitivity of the thromboplastin reagent, called an international sensitivity index (ISI). Warfarin and heparin therapies are overlapped for several days in humans because when coumarin treatment is initiated, the level of protein C (a naturally occurring antithrombotic protein) is decreased, creating a thrombogenic potential. Over-

lapping heparin therapy theoretically counteracts this transient procoagulant effect before other vitamin K–dependent factors (factors II, IX, and X) are affected by warfarin.[430–432] The necessity for this maneuver in cats has not been established. Warfarin has been proposed by some cardiologists for chronic oral maintenance in cases of advanced myocardial disease. Most advise caution, or reserve it for cases of actual arterial embolism in indoor cats with attentive owners. Cefazolin, ketoconazole, metronidazole, neomycin, tetracycline, vitamin E, trimethoprim-sulfamethoxazole, and miconazole can potentially increase the effect of warfarin.[433] Catastrophic hemorrhage is a potential complication of coumarin therapy (Fig. 28–37).

ANTIPLATELET AGGREGATION

RATIONALE. Exposure of blood to subendothelial connective tissue leads to rapid platelet activation, formation of platelet plugs, and subsequent thrombus. Primary prevention is necessary since prothrombotic factors are prevalent in feline cardiomyopathy, and because prognosis for the treatment of thromboembolism is poor. Pharmacologic measures are directed to modify platelet aggregation.

ASPIRIN. Aspirin can be used based upon its theoretical benefit during and after a thromboembolic episode to prevent further embolic events. Aspirin induces a functional defect in platelets by irreversibly inactivating (through acetylation) cyclo-oxygenase, an enzyme critical for converting arachidonic acid to thromboxane A_2,[434–436] and which in the vascular wall is responsible for converting arachidonic acid to prostacyclin.[436–438] Thromboxane A_2 induces platelet activation (through release of platelet adenosine diphosphate) and vasoconstriction (as does serotonin), whereas prostacyclin inhibits platelet aggregation and induces vasodilation.[400, 439] The aspirin-induced acetylation of the cyclo-oxygenase enzyme is irreversible and persists for the life of the platelet, which is 7 to 10 days, as does platelet aggregation and release response to various agonists.

In cats, aspirin (25 mg/kg, or ¼ of a 5-grain tablet q48–72h PO) effectively inhibits platelet function for 3 to 5 days and is relatively safe.[440–442] Improved collateral circulation has been demonstrated in aspirin-treated cats with experimentally created aortic thrombosis.[419] Concern regarding potential inhibition of prostacyclin by aspirin is not unfounded.[436, 443] The optimal aspirin dose that will inhibit thromboxane A_2 production but spare vascular endothelial prostacyclin synthesis has not yet been established for cats. Because the value of aspirin in preventing a first occurrence of cardiogenic emboli is unknown, and its value in preventing thrombus recurrence in cats with previous emboli is doubtful, there is need for clinical trials to assess this therapy. Side effects of aspirin are mainly gastrointestinal and can be severe with overdosage.

AMPUTATION

In situations of irreversible loss of limb viability, particularly limb necrosis, amputation provides an alternative to euthanasia when all other patient parameters are stable (Fig. 28–38). In selected cases, good quality of life has been achieved for up to 1 year postamputation, although repeated systemic embolization must be anticipated and is a limitation for long-term success. It should be noted that some cats who survive severe saddle embolus incur severe atrophy of their cranial tibial muscle group and sustain permanent flexure of their metatarsus (Fig. 28–36). Such patients, when cared for using a soft, padded protec-

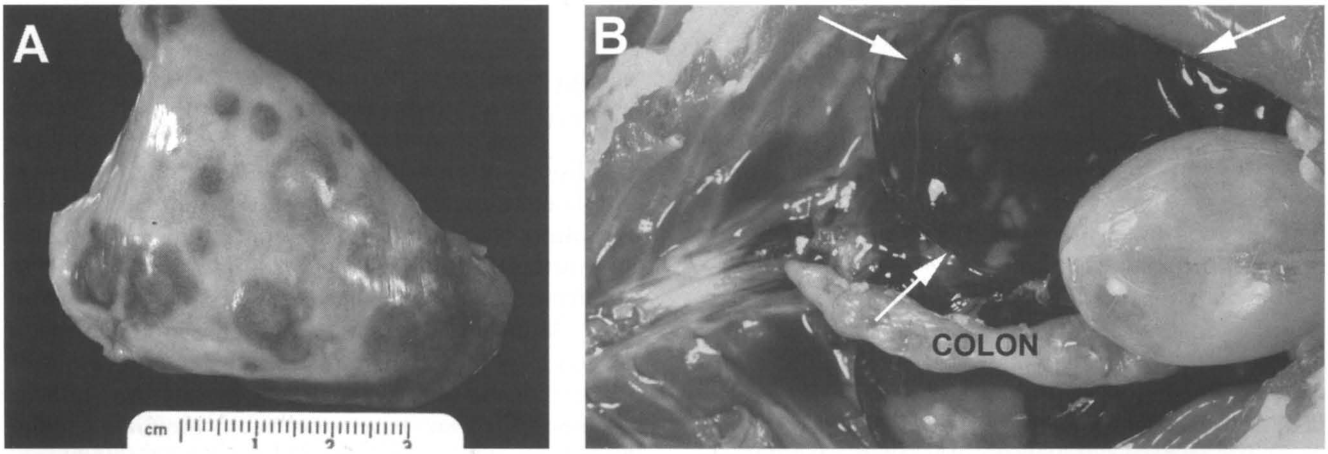


FIGURE 28–37

Postmortem of a cat that became acutely anemic and died while maintained on warfarin anticoagulation therapy. (A) The lungs contained multiple large areas of hemorrhage. (B) In addition to hemoabdomen, severe retroperitoneal bleeding had occurred (outlined by arrows adjacent to the colon and bladder).

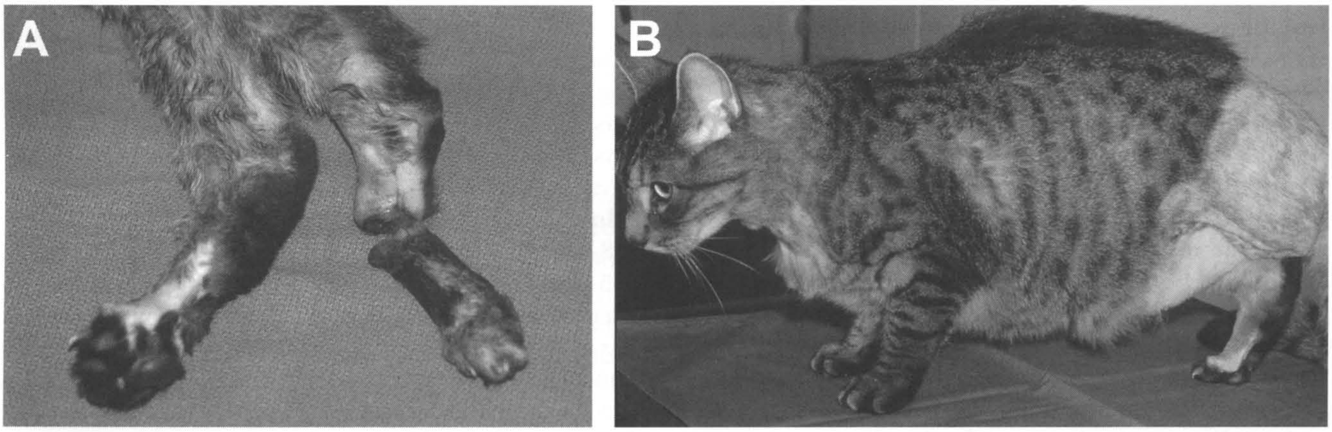


FIGURE 28–38

Cat with restrictive cardiomyopathy with a saddle embolism and heart failure. During the first week post embolization, the pet chewed and mutilated its distal extremities. The wounds filled with granulation tissue and slowly healed by second intention over an eight-week period. (A) Despite medical therapies, the distal left metatarsus became lichenified by about six weeks post embolization. These lesions progressed to avascular necrosis resulting in pathologic fracture and distraction at the proximal metatarsal region. (B) The left rear leg was amputated and the cat survived eight months before experiencing a second saddle embolism.

tive bandage on the distal limb, may bear weight on the leg and otherwise achieve a good quality of life.

SUPPORTIVE AND ADJUNCTIVE MEASURES

Aspirin is administered for myalgia associated with ischemic myopathy, in addition to antiplatelet effects. Epidural analgesia with morphine (0.05 to 0.1 mg/kg one time) can be safe and effective when administered within the first 12 to 18 hours after embolization. Most affected cats are anorectic, dehydrated, and hypokalemic. It is important to maintain hydration, electrolyte balance, and nutritional support. If CHF has been resolved and the cat remains anorectic, placement of a nasoesophageal feeding tube is advocated for alimentation, particularly during the first week of therapy. Self-mutilation of distal limbs devitalized by an occlusive saddle embolus is commonly exhibited during convalescence and is characterized by excessive licking or chewing of the toes or lateral hock. Application of a loose-fitting bandage, stockinette, or other barrier is usually effective. Placement of indwelling venous catheters into veins of legs devitalized by occlusive embolus should always be avoided.

PATIENT MONITORING

Clinical pathology evaluations are dictated by patient status. Biochemical profiles are useful to assess renal function and electrolyte status, and coagulation profiles (APTT, partial thromboplastin time [PTT], FSP, platelet count) are needed to evaluate anticoagulation therapy and detect disseminated intravascular coagulation. Sudden hyperkalemia can result from *reperfusion syndrome* (ischemic rhabdomyolysis and reperfusion) when arterial blood flow is re-established to a previously ischemic region, resulting in acute catastrophic release of potassium into the systemic circulation. Since this may occur without warning, continuous ECG monitoring of hospitalized cats with thromboembolism is a useful, safe, and cost efficient method to detect large increases in serum potassium concentration. Sequential ECG changes become evident, including P-R interval prolongation and gradual disappearance of P waves, widening of the QRS complex, increasing T-wave amplitude, and bradycardia. Fatal bradyarrhythmias progressing to asystole appear to be the mode of death in these hyperkalemic cats.[115] Standard therapies for hyperkalemia may be attempted[444] but have been unrewarding. Aggressive measures to reduce and maintain serum potassium have been successful in a few cases by initial IV administration of sodium bicarbonate, followed by titrated doses of regular insulin and glucose administered by constant-rate infusion.

PRIMARY PREVENTION OF THROMBOEMBOLISM

Although aspirin has been demonstrated to exert antiplatelet aggregating properties to feline platelets *in vitro,* there are no data to support routine prophylactic administration to cats with cardiomyopathy unless countervailing risk factors (see earlier) have been identified. Multicenter clinical trials have not been performed to evaluate preventive strategies.

Effective recommendations for prevention of arterial thromboembolism have not been identified. Antithrombotic approaches should be based upon concepts of pathogenesis and an appreciation of relative risks. Large-scale studies are needed to evaluate epidemiology, risk factors, etiopathogenesis, and natural history of cardiomyopathy and systemic embolism. Cur-

rent data indicate that arterial emboli originate from the heart and therefore represent a cardiac disorder. Cardiomyopathies commonly progress to evolve similar pathophysiologic end-points that favor thrombosis due to a triad of precipitating factors identified by Virchow over a century ago: endothelial injury, a zone of circulatory stasis, and a hypercoagulable state (see Pathophysiology, earlier). Therefore, primary prevention of thromboembolism is basically a battle against the underlying cardiac disorder. No therapies have been identified that reverse or significantly retard the development of feline heart disease or its related pathologic or prothrombotic sequelae. Moreover, it is likely that multiple interactions are involved in thrombogenesis, including myocardial pathology and cardiac dysfunction, platelets, and other blood components and factors.

REFERENCES

1. Wynne JW, Braunwald, E. The cardiomyopathies and myocarditides. *In* Braunwald E (ed): Heart Disease; A Textbook of Cardiovascular Medicine. 5th ed. Philadelphia, WB Saunders, 1997, p 1404
2. Goodwin JF. Cardiomyopathies and specific heart muscle diseases. Definitions, terminology, classifications and new and old approaches. Postgrad Med J 68:S3, 1992
3. Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. Circulation 93:841, 1996
4. Fox PR. Myocardial diseases. *In* Ettinger SJ (ed): Textbook of Veterinary Internal Medicine; Diseases of the Dog and Cat. 3rd ed. Philadelphia, WB Saunders, 1989, p 1097
5. Fox PR. Feline myocardial disease. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 435
6. Sisson DD, Thomas W. Myocardial diseases. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine; Diseases of the Dog and Cat. 4th ed. Philadelphia, WB Saunders, 1995, p 995
7. Fox PR. Feline myocardial diseases. *In* Kirk RW (ed): Current Veterinary Therapy. Vol VIII. Philadelphia, WB Saunders, 1983, p 337
8. Kushwaha SS, Fallon JT, Fuster V. Restrictive cardiomyopathy. N Engl J Med 336:267, 1997

8a. Keren A, Popp RL. Assignment of patients into the classification of cardiomyopathies. Circulation 86:1622, 1992

9. Liu SK. Pathology of feline heart disease. Vet Clin North Am 7:323, 1977
10. Maron BJ, Spirito P. Impact of patient selection biases on the perception of hypertrophic cardiomyopathy and its natural history. Am J Cardiol 72:970, 1993
11. Fananapazir L, Epstein ND. Prevalence of hypertrophic cardiomyopathy and limitations of screening methods. Circulation 92:700, 1995
12. Choong CY. Left ventricle V. Diastolic function—its principles and evaluation. *In* Weyman AE (ed): Principles and Practice of Echocardiography. 2nd ed. Philadelphia, Lea & Febiger, 1994, p 721
13. Golden AL, Bright JM. Use of relaxation half-time as an index of ventricular relaxation in clinically normal cats and cats with hypertrophic cardiomyopathy. Am J Vet Res 51:1352, 1990
14. Levine RA. Echocardiographic assessment of the cardiomyopathies. *In* Weyman AE (ed): Principles and Practice of Echocardiography. 2nd ed. Philadelphia, Lea & Febiger, 1994, p 781
15. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinicians' Rosetta stone. J Am Coll Cardiol 30:8, 1997
16. Gilbert JC, Glantz SA. Determinants of left ventricular filing and the diastolic pressure-volume relation. Circ Res 64:827, 1989
17. Little WC, Downes TR. Clinical evaluation of left ventricular diastolic performance. Prog Cardiovasc Dis 32:273, 1990
18. Brutsaert DL. Nonuniformity: a physiologic modulator of contraction and relaxation of the normal heart. J Am Coll Cardiol 9:341, 1987
19. Brutsaert DL, Rademakers FE, Sys SU, et al. Analysis of relaxation in the evaluation of ventricular function of the heart. Prog Cardiovasc Dis 28:143, 1985
20. Brutsaert DL, Rademakers FE, Sys SU. Triple control of relaxation: implication in cardiac disease. Circulation 69:190, 1984
21. Van Vleet JF, Ferrans V. Myocardial diseases of animals. Am J Pathol 124:97, 1986
22. Liu SK, Fox PR, Tilley LP. Excessive moderator bands in the left ventricle of 21 cats. J Am Vet Med Assoc 180:1215, 1982
23. Liu SK, Peterson ME, Fox PR. Hypertrophic cardiomyopathy and hyperthyroidism in the cat. J Am Vet Med Assoc 185:52, 1984
24. Tilley LP, Liu SK, Gilbertson SR, et al. Primary myocardial disease in the cat: a model for human cardiomyopathy. Am J Pathol 87:493, 1977
25. Fox PR, Liu SK, Maron BJ. Echocardiographic assessment of spontaneously occurring feline hypertrophic cardiomyopathy: an animal model of human disease. Circulation 92:2645, 1995
26. Liu SK, Roberts WC, Maron BJ. Comparison of morphologic findings in spontaneously occurring hypertrophic cardiomyopathy in humans, cats and dogs. Am J Cardiol 72:944, 1993

26a. Maron BJ, Bonow RO, Cannon RO III, et al. Hypertrophic cardiomyopathy; interrelations of clinical manifestations, pathophysiology, and therapy (first of two parts). N Engl J Med 316:844, 1987

27. Nishimura RA, Housmans PR, Hatle LK, et al. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography. Mayo Clin Proc 64:71, 1989
28. Appleton CP, Hatle LK. The natural history of left ventricular filling abnormalities: assessment of two-dimensional and Doppler echocardiography. Echocardiography 9:437, 1992
29. Appleton CP, Hatle LK, Popp RL. Demonstration of restrictive ventricular physiology by Doppler echocardiography. J Am Coll Cardiol 11:757, 1988
30. Maron BJ, Spirito P, Green KJ, et al. Noninvasive assessment of left ventricular diastolic function by pulsed Doppler echocardiography in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 10:733, 1987

31. Pozzoli M, Traversi E, Cioffi G, et al. Loading manipulations improve the prognostic value of Doppler evaluation of mitral flow in patients with chronic heart failure. Circulation 95:1222, 1997
32. Harrison MR, Clifton GD, Pennell AT, et al. Effect of heart rate on left ventricular diastolic transmitral flow velocity patterns assessed by Doppler echocardiography in normal subjects. Am J Cardiol 67:622, 1991
33. Atkins CE, Gallo AM, Kurzman ID, et al. Risk factors, clinical signs, and survival in cats with a clinical diagnosis of idiopathic hypertrophic cardiomyopathy: 74 cases (1985–1989). J Am Vet Med Assoc 201:603, 1992
34. Fox PR, Tilley LP, Liu SK. The cardiovascular system. *In* Pratt PW (ed): Feline Medicine. Santa Barbara, CA, American Veterinary Publications, 1983, p 249
35. Harpster NK. The cardiovascular system. *In* Holzworth J (ed): Diseases of the Domestic Cat. Vol I. Philadelphia, WB Saunders, 1986, p 820
36. Van Vleet J, Ferrans VJ, Weirich WE. Pathologic alterations in hypertrophic and congestive cardiomyopathy of cats. Am J Vet Res 41:2037, 1980
37. Harpster NK. Feline myocardial diseases. *In* Kirk RW (ed): Current Veterinary Therapy. Vol IX. Philadelphia, WB Saunders, 1986, p 380
38. Martin L, VandeWoude S, Boon J, et al. Left ventricular hypertrophy in a closed colony of Persian cats. Abstract. J Vet Intern Med 8:143, 1994
39. Kittleson MD, Meurs KM, Kittleson J, et al. Heritable characteristics, phenotypic expression, and natural history of hypertrophic cardiomyopathy in Maine coon cats; Abstract. J Vet Intern Med 12:198, 1998
40. Kittleson MD, Kittleson JA, Mekhamer Y. Development and progression of inherited hypertrophic cardiomyopathy in Maine coon cats. Abstract. J Vet Intern Med 10:165, 1996
41. Meurs K, Kittleson MD, Towbin J, et al. Familial systolic anterior motion of the mitral valve and/or hypertrophic cardiomyopathy is apparently inherited as an autosomal dominant trait in a family of American shorthair cats. Abstract. J Vet Intern Med 11:138, 1997
42. Seidman CE, Seidman JG. Gene mutations that cause familial hypertrophic cardiomyopathy. *In* Hager E (ed): Scientific American Molecular Cardiovascular Medicine. New York, Scientific American, Inc, 1995, p 193
43. Marian AJ, Roberts R. Recent advances in the molecular genetics of hypertrophic cardiomyopathy. Circulation 92:1336, 1995
44. Kimura A, Harada H, Park J-E, et al. Mutations in the cardiac troponin I gene associated with hypertrophic cardiomyopathy. Nature Genetics 16:379, 1997
45. Marian AJ, Yu Q-T, Mann FL, et al. Expression of a mutation causing hypertrophic cardiomyopathy disrupts sarcomere assembly in adult feline cardiac myocytes. Circ Res 77:98, 1995
46. Solomon SD, Simonetta W, Watkins H, et al. Left ventricular hypertrophy and morphology in familial hypertrophic cardiomyopathy associated with mutations of the beta-myosin heavy chain gene. J Am Coll Cardiol 22:498, 1993
47. Solomon SD, Jarcho JA, McKenna W, et al. Familial hypertrophic cardiomyopathy is a genetically heterogeneous disease. J Clin Invest 86:993, 1990
48. Charron P, Dubourg O, Desnos M, et al. Clinical features and prognostic implications of familial hypertrophic cardiomyopathy related to the cardiac myosin-binding protein C gene. Circulation 97:2230, 1998
49. Watkins H, Thierfelder L, Hwang D-S, et al. Sporadic hypertrophic cardiomyopathy due to de novo myosin mutations. J Clin Invest 90:1666, 1992
50. Zak R. Molecular mechanisms of cardiac hypertrophy. *In* Hager E (ed): Scientific American Molecular Cardiovascular Medicine. New York, Scientific American, Inc, 1995, p 177
51. Lechin M, Quinones MA, Omran A, et al. Angiotensin-I converting enzyme genotypes and left ventricular hypertrophy in patients with hypertrophic cardiomyopathy. Circulation 92:1808, 1995
52. Hayashida W, Kumada T, Kohno F, et al. Left ventricular regional relaxation and its nonuniformity in hypertrophic nonobstructive cardiomyopathy. Circulation 84:1496, 1991
53. Betocci S, Hess OM, Losi MA, et al. Regional left ventricular mechanics in hypertrophic cardiomyopathy. Circulation 88:2206, 1993
54. Spirito P, Maron BJ. Relation between extent of left ventricular hypertrophy and diastolic filling abnormalities in hypertrophic cardiomyopathy. J Am Coll Cardiol 15:808, 1990
55. Briguori C, Betocchi S, Losi MA, et al. Noninvasive evaluation of left ventricular diastolic function in hypertrophic cardiomyopathy. Am J Cardiol 81:180, 1998
56. Bright JM, Golden L, Gompf R, et al. Evaluation of the calcium channel-blocking agents diltiazem and verapamil for treatment of feline hypertrophic cardiomyopathy. J Vet Intern Med 5:272, 1991
57. Bright JM, Hertage ME. Pulsed Doppler assessment of left ventricular diastolic function in normal and cardiomyopathic cats. Proc 15th Annu Vet Med Forum, 1997, p 212
58. Losi MA, Betocci S, Grimaldi M, et al. Heterogeneity of left ventricular filling dynamics in hypertrophic cardiomyopathy. Am J Cardiol 73:987, 1990
59. Wiggle ED. Impaired left ventricular relaxation in hypertrophic cardiomyopathy: relation to extent of hypertrophy. J Am Coll Cardiol 15:814, 1990
60. Gwathmey JK, Warren SE, Briggs GM, et al. Diastolic dysfunction in hypertrophic cardiomyopathy. Effect on active force generation during systole. J Clin Invest 87:1023, 1991
61. Stauffer JC, Gaasch WH. Recognition and treatment of left ventricular diastolic dysfunction. Prog Cardiovasc Dis 32:319, 1990
62. Factor SF, Butany J, Sole MJ, et al. Pathologic fibrosis and matrix connective tissue in the subaortic myocardium of patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 17:13434, 1991
63. Dilsizian V, Bonow RO, Epstein SE, et al. Myocardial ischemia detected by thallium scintigraphy is frequently related to cardiac arrest and syncope in young patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 22:796, 1993
64. Grossman W, McLaurin LP. Diastolic properties of the left ventricle. Ann Intern Med 84:316, 1974
65. Maron BJ, Wolfson JK, Epstein SE, et al. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. J Am Cardiol 8:545, 1986
66. Tanaka M, Fuijiwara H, Onodera T, et al. Quantitative analysis of narrowing of intramyocardial small arteries in normal heart, hypertensive hearts, and hearts with hypertrophic cardiomyopathy. Circulation 75:1130, 1987
67. Liu SK. The intramural coronary arterial lesions in 102 cats with hypertrophic cardiomyopathy. Abstract. Sci Proc Internat Acad Pathol, 1989, p 54
68. Krams R, Kofflard MJM, Duncker DJ, et al. Decreased coronary flow reserve in hypertrophic cardiomyopathy is related to remodeling of the coronary microcirculation. Circulation 97:230, 1998

68a. Schwartzkopff B, Mundhenke M, Strauer BE. Alterations of the architecture of subendocardial arterioles in patients with hypertrophic cardiomyopathy and impaired coronary vasodilator reserve: a possible cause for myocardial ischemia. J Am Coll Cardiol 31:1089, 1998
68b. Jung W-I, Sieverding L, Breuer J, et al. ^{31}P NMR spectroscopy detects metabolic abnormalities in asymptomatic patients with hypertrophic cardiomyopathy. Circulation 97:2536, 1998
69. Lord PF, Wood A, Tilley LP. Radiographic and hemodynamic evaluation of cardiomyopathy and thromboembolism in the cat. J Am Vet Med Assoc 164:154, 1974
70. Sarnoff SJ, Braunwald E, Welch GH Jr, et al. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. Am J Physiol 192:148, 1958
71. Boerth RC, Covell JW, Pool PE, et al. Increased myocardial oxygen consumption and contractile state associated with increased heart rate in dogs. Circ Res 24:725, 1969
72. Cannon RO III, Rosing DR, Maron BJ, et al. Myocardial ischemia in patients with hypertrophic cardiomyopathy: contribution of inadequate vasodilator reserve and elevated left ventricular filling pressures. Circulation 71:234, 1985
72a. Peters NS, Wit AL. Myocardial architecture and ventricular arrhythmogenesis. Circulation 97:1746, 1998
73. Levine RA, Lefebvre X, Guerrero JL, et al. Unifying concepts of mitral valve function and disease: SAM, prolapse and ischemic mitral regurgitation. J Cardiol 24 (Suppl 38):15, 1994
74. Sherrid MV, Pearle G, Gunsburg DZ. Mechanism of benefit of negative inotropes in obstructive hypertrophic cardiomyopathy. Circulation 97:41, 1998
75. Wigle ED, Rakowski H, Kimball BP, et al. Hypertrophic cardiomyopathy: clinical spectrum and treatment. Circulation 92:1680, 1995
76. Nakatani S, Schwammenthal E, Lever HM, et al. New insights into the reduction of mitral valve systolic anterior motion after ventricular septal myectomy in hypertrophic obstructive cardiomyopathy. Am Heart J 131:294, 1996
77. Lin C-S, Chen K-S, Lin M-C, et al. The relationship between systolic anterior motion of the mitral valve and the left ventricular outflow tract Doppler in hypertrophic cardiomyopathy. Am Heart J 122:1671, 1991
78. Spirito P, Maron BJ, Rosing DR. Morphologic determinants of hemodynamic state after ventricular septal myotomy-myectomy in patients with obstructive hypertrophic cardiomyopathy: M-mode and two-dimensional echocardiographic assessment. Circulation 70:84, 1984
79. Jiang L, Levine RA, King ME, et al. An integrated mechanism to explain the systolic anterior motion of the mitral valve in hypertrophic cardiomyopathy based on echocardiographic observations. Am Heart J 113:633, 1987
80. Murgo JP. The hemodynamic evaluation in hypertrophic cardiomyopathy: systolic and diastolic dysfunction. Cardiovasc Clin 19:193, 1988
81. Knight C, Kurbaan AS, Seggewiss H, et al. Nonsurgical septal reduction for hypertrophic obstructive cardiomyopathy: outcome in the first series of patients. Circulation 95:2075, 1997
82. Sasson Z, Yock PG, Hatle LK, et al. Doppler echocardiographic determination of the pressure gradient in hypertrophic cardiomyopathy. J Am Coll Cardiol 11:752, 1988
83. Spirito P, Seidman CE, McKenna WJ, et al. The management of hypertrophic cardiomyopathy. N Engl J Med 336:775, 1997
84. Pai RG, Jintapakorn W, Tanimoto M, et al. Role of papillary muscle position and mitral valve structure in systolic anterior motion of the mitral leaflets in hyperdynamic left ventricular function. Am J Cardiol 76:623, 1995
85. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. J Am Coll Cardiol 26:1699, 1995
86. Klues HG, Roberts WC, Maron BJ. Morphological determinants of echocardiographic patterns of mitral valve systolic anterior motion in obstructive hypertrophic cardiomyopathy. Circulation 87:1570, 1993
87. Gilligan DM, Chan WL, Stewart R, et al. Cardiac responses assessed by echocardiography to changes in preload in hypertrophic cardiomyopathy. Am J Cardiol 73:312, 1994
88. McCully RB, Nishimura RA, Tajik AJ, et al. Extent of clinical improvement after surgical treatment of hypertrophic obstructive cardiomyopathy. Circulation 94:467, 1996
89. Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. J Am Coll Cardiol 12:426, 1988
90. Oki T, Fukuda N, Luchi A, et al. Transesophageal echocardiographic evaluation of mitral regurgitation in hypertrophic cardiomyopathy: contributions of eccentric left ventricular hypertrophy and related abnormalities of the mitral complex. J Am Soc Echocardiogr 8:503, 1995
90a. Yonezawa Y, Nihoyannopoulos P, McKenna WJ, et al. Mitral regurgitation in hypertrophic cardiomyopathy; a color Doppler echocardiographic study. Am J Noninvas Cardiol 2:195, 1988
91. Bonagura JD, Stepien RL, Lehmkuhl LB. Acute effects of esmolol on left ventricular outflow obstruction in cats with hypertrophic cardiomyopathy: a Doppler-echocardiographic study. Abstract. J Vet Intern Med 5:123, 1991
92. Rishniw M, Thomas WP, Kienle RD. Dynamic right midventricular obstruction in 50 cats. Abstract. J Vet Intern Med 10:159, 1996
93. Maron GJ, McIntosh CL, Klues HG, et al. Morphologic basis for obstruction to right ventricular outflow in hypertrophic cardiomyopathy. Am J Cardiol 71:1098, 1993
94. Dong S-J, MacGregor JH, Crawley AP, et al. Left ventricular wall thickness and regional systolic function in patients with hypertrophic cardiomyopathy A three-dimensional tagged magnetic resonance imaging study. Circulation 90:1200, 1994
95. Kramer C, Reickek N, Ferrari VA, et al. Regional heterogeneity of function in hypertrophic cardiomyopathy. Circulation 90:186, 1994
95a. Maron BJ, Spirito P. Implications of left ventricular remodeling in hypertrophic cardiomyopathy. Am J Cardiol 81:1339, 1998
96. Spirito P, Maron BJ, Bonow RO, et al. Occurrence and significance of progressive left ventricular wall thinning and relative cavity dilation in hypertrophic cardiomyopathy. Am J Cardiol 59:123, 1987
97. Seiler C, Jenni R, Vassalli G, et al. Left ventricular

chamber dilatation in hypertrophic cardiomyopathy: related variables and prognosis in patients with medical and surgical therapy. Br Heart J 74:508, 1995
98. Kawano S, Iida K, Fujieda K, et al. Response to isoproterenol as a prognostic indicator of evolution from hypertrophic cardiomyopathy to a phase resembling dilated cardiomyopathy. J Am Coll Cardiol 25:687, 1995
99. Liu SK, Maron BJ, Tilley LP. Feline hypertrophic cardiomyopathy: gross anatomic and quantitative histologic features. Am J Pathol 102:388, 1981
99a. Maron BJ, Gottdiener JS, Epstein SE. Patterns and significance of distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a wide-angle, two-dimensional echocardiographic study of 125 patients. Am J Cardiol 48:418, 1981
100. Bright JM, Golden AL, Daniel GB. Feline hypertrophic cardiomyopathy: variations on a theme. J Small Anim Pract 33:66, 1992
101. Peterson EN, Moise NS, Brown CA, et al. Heterogeneity of hypertrophic cardiomyopathy in feline hypertrophic heart disease. J Vet Intern Med 7:183, 1993
102. Maron BJ, Roberts WC. Quantitative analysis of cardiac muscle cell disorganization in the ventricular septum of patients with hypertrophic cardiomyopathy. Circulation 59:689, 1979
103. St John Sutton MG, Lie JT, Anderson KR, et al. Histopathological specificity of hypertrophic obstructive cardiomyopathy: myocardial fibre disarray and myocardial fibrosis. Br Heart J 44:433, 1980
104. Liu SK, Fox PR. Myocardial ischemia and infarction. *In* Kirk RW, Bonagura JD (eds): Kirk's Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1002, p 791
105. Maron BJ, Epstein SE, Roberts WC. Hypertrophic cardiomyopathy and transmural myocardial infarction without significant atherosclerosis of the extramural coronary arteries. Am J Cardiol 43:1086, 1979
106. Bonagura JD. Cardiovascular diseases. *In* Sherding RG (ed): The Cat. Diseases and Clinical Management. 2nd ed. New York, Churchill Livingstone, 1994, p 819
107. Fox PR, Broussard JD, Peterson ME. Electrocardiographic and radiographic changes in cats with hyperthyroidism: comparison of populations evaluated during 1979–1982 vs. 1992–1993. Abstract. J Vet Intern Med 7:118, 1993
108. Kittleson ME. Feline hypertrophic cardiomyopathy. *In* Bonagura JD (ed): Kirk's Current Veterinary Therapy. Vol XII. Philadelphia, WB Saunders, 1995, p 854
109. Fox PR, Kaplan P. Feline arrhythmias. Contemp Issues Small Anim Pract 7:251, 1987
110. Bond BR, Fox PR. Advances in feline cardiomyopathy. Vet Clin North Am 14:1021, 1984
111. Fox PR, Bond BR. Nonselective and selective angiocardiography. Vet Clin North Am 13:259, 1983
112. Fox PR. Feline cardiomyopathy. Contemp Issues Small Anim Pract 7:157, 1987
113. Wilkins RJ. Clinical pathology of feline cardiac disease. Vet Clin North Am 7:285, 1977
113a. Fox PR. Current usage and hazards of diuretic therapy. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1992, p 668
114. Kittleson MD, Pion PD, DeLellis LA, et al. Increased serum growth hormone concentration in feline hypertrophic cardiomyopathy. J Vet Intern Med 6:320, 1992
115. Fox PR, Moïse NS, Price RA, et al. Analysis of continuous ECG (Holter) monitoring in normal cats and cardiomyopathic cats in congestive heart failure. Abstract. J Vet Intern Med 12:199, 1998
116. Brater DC. The use of diuretics in congestive heart failure. Semin Nephrol 14:479, 1994.
117. Philbin EF, Cotto M, Rocco TA, et al. Association between diuretic use, clinical response, and death in acute heart failure. Am J Cardiol 80:519, 1997
117a. Burnier M, Brunner HR. Neurohormonal consequences of diuretics in different cardiovascular syndromes. Eur Heart J 13(Suppl G):28, 1992
118. von Dohlen TW, Prisant LM, Frank MJ. Significance of positive or negative thallium-201 scintigraphy in hypertrophic cardiomyopathy. Am J Cardiol 64:498, 1989
119. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. J Am Med Assoc 270:1589, 1993
120. Kennedy HL, Brooks MM, Barker AH, et al. Beta-blocker therapy in the Cardiac Arrhythmia Suppression Trial. Am J Cardiol 74:674, 1994
121. ISIS-1 (first International Study of Infarct Survival) Collaborative Group. Mechanisms for the early mortality reduction produced by beta blockade started early in acute myocardial infarction. Lancet 1:921, 1988
122. Yusuf S, Peto R, Lewis J, et al. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 27:335, 1985
123. Barron HV, Viskin S, Lundstrom RJ, et al. Beta-blocker dosages and mortality after myocardial infarction. Arch Intern Med 158:449, 1998
124. Clarkson PBM, Wheeldon NM, Macleod C, et al. Systolic and diastolic effects of beta-adrenergic stimulation in normal humans. Am J Cardiol 75:206, 1997
125. Dujardin KS, Enriquez-Sarano M, Rossi A, et al. Echocardiographic assessment of left ventricular remodeling: are left ventricular diameters suitable tools? J Am Coll Cardiol 30:1534, 1997
126. Foy SG, Crozier IG, Turner JG, et al. Comparison of enalapril vs captopril on left ventricular function and survival three months after acute myocardial infarction (The "PRACTICAL" Study). Am J Cardiol 73:1180, 1994
127. Køber L, Torp-Pedersen C, on behalf of the TRACE Study Group. Clinical characteristics and mortality of patients screened for entry into the transolapril cardiac evaluation (TRACE) study. Am J Cardiol 76:1, 1995
128. Greenberg B, Quinones MA, Koilpillai C, et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD Echocardiographic Substudy. Circulation 91:2573, 1995
129. Torp-Pedersen C, Køber L, Burchardt H. The place of angiotensin-converting enzyme inhibition after acute myocardial infarction. Am Heart J 134:S25, 1997
130. Latini R, Maggioni AP, Flather M, et al. ACE-inhibitor use in patients with myocardial infarction: summary of evidence from clinical trials. Circulation 32:3232, 1995
131. Rutherford JD, Pfeffer MA, Moye LA, et al. Effects of captopril on ischemic events after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. Circulation 90:1731, 1994
132. Skolnick AE, Frishman WH. Calcium channel blockers in myocardial infarction. Arch Intern Med 149:1669, 1989
133. Hager WD, Davis BR, Riba A, et al. Absence of a deleterious effect of calcium channel blockers in patients with left ventricular dysfunction after myocardial infarction: the SAVE study experience. Am Heart J 135:406, 1998
134. Multicenter Postinfarction Trial (MDPIT) Research Group. The effect of diltiazem on mortality and rein-

farction after myocardial infarction. N Engl J Med 319:385, 1988
135. Ishikawa K, Nakai S, Takenaka T, et al. Short-acting nifedipine and diltiazem do not reduce the incidence of cardiac events in patients with healed myocardial infarction. Circulation 95:2368, 1997
136. Kostis JV, Lacy CR, Cosgrove RN, et al. Association of calcium channel blocker use with increased rate of acute myocardial infarction in patients with left ventricular dysfunction. Am Heart J 133:550, 1997
137. Packer M. Calcium channel blockers in chronic heart failure: the risk of "physiological rationale" therapy. Circulation 82:2254, 1990
138. ACC/AHA guidelines for the management of patients with acute myocardial infarction. J Am Coll Cardiol 78:153, 1996
139. Messerli FH, Michalewicz L. Safety of heart rate–lowering calcium antagonists: lessons from controlled trials. Am Heart J 134 (Suppl):S21, 1997
140. Boyden PA, Tilley LP, Albala A, et al. Mechanisms for atrial arrhythmias associated with cardiomyopathy: a study of feline hearts with primary myocardial disease. Circulation 69:036, 1984
141. Liu SK, Tilley LP. Animal models of primary myocardial diseases. Yale J Biol Med 53:191, 1980
142. Kimura S, Bassett AL, Cameron JS, et al. Cellular electrophysiological changes during ischemia in isolated, coronary-perfused cat ventricle with healed myocardial infarction. Circulation 78:401, 1988
142a. Stevenson WG, Stevenson LW, Middlekauff HR, et al. Sudden death prevention in patients with advanced ventricular dysfunction. Circulation 88:2953, 1993
143. Maron B, Shirani J, Poliac LC, et al. Sudden death in young competitive athletes; clinical, demographic, and pathological profiles. J Am Med Assoc 276:199, 1996
144. Wigle ED. Novel insights into the clinical manifestations and treatment of hypertrophic cardiomyopathy. Curr Opin Cardiol 10:29, 1995
145. Yetman AT, McCrindle BW, MacDonald C, et al. Myocardial bridging in children with hypertrophic cardiomyopathy—a risk factor for sudden death. N Engl J Med 339:1201, 1998
146. Bristow MR. Mechanism of action of beta-blocking agents in heart failure. Am J Cardiol 80:26L, 1997
147. Cody RJ. The sympathetic nervous system and the renin-angiotensin-aldosterone system in cardiovascular diseases. Am J Cardiol 80:9J, 1997
148. Maron BJ, Bonow RO, Cannon RO III, et al. Hypertrophic cardiomyopathy. Interrelations of clinical manifestations, pathophysiology and therapy (second of two parts). N Engl J Med 316:780, 1987
149. Heidenreich PA, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. J Am Coll Cardiol 30:27, 1997
150. Bonow RO. Left ventricular diastolic function in hypertrophic cardiomyopathy. Herz 16:13, 1991
151. Gistri R, Cecchi F, Choudhury L, et al. Effect of verapamil on absolute myocardial blood flow in hypertrophic cardiomyopathy. Am J Cardiol 74:363, 1994
152. Rials SJ, Wu Y, Pauletto FJ, et al. Effect of an intravenous angiotensin-converting enzyme inhibitor on the electrophysiologic features of normal and hypertrophied feline ventricles. Am Heart J 132:989, 1996
153. Pfeffer MA, Pfeffer JM. Pharmacologic regression of cardiac hypertrophy in experimental hypertension. J Cardiovasc Pharmacol 6:S865, 1989
154. Dell'Itallia LJ, Oparil S. Cardiac renin angiotensin system in hypertrophy and the progression to heart failure. Heart Failure Rev 1:63, 1966
155. Oshikawa T, Handa S, Anzai T, et al. Early reduction of neurohumoral factors plays a key role in mediating the efficacy of β-blocker therapy for congestive heart failure. Am Heart J 131:329, 1996
156. Rush JE, Freeman LM, Brown DJ, et al. The use of enalapril in the treatment of feline hypertrophic cardiomyopathy. J Am Anim Hosp Assoc 34:88, 1998
157. Maron BJ, Roberts WC, Epstein SE. Sudden cardiac death in hypertrophic cardiomyopathy: a profile in 78 patients. Circulation 65:1388, 1982
158. Maron BJ, Cecchi F, McKenna WJ. Risk factors and stratification for sudden death in patients with hypertrophic cardiomyopathy. Br Heart J 72:S13, 1994
159. Schiavone WA, Malone JD, Lever HD, et al. Electrophysiologic studies of patients with hypertrophic cardiomyopathy with syncope of undetermined etiology. Pacing Clin Electrophysiol 9:476, 1989
159a. Nienaber CA, Hiller S, Spielmann RP, et al. Syncope in hypertrophic cardiomyopathy: multivariate analysis of prognostic determinants. J Am Coll Cardiol 15:948, 1990
160. McAreavey D, Dilsizian V, Panza J, et al. Favorable prognosis in 88 young hypertrophic cardiomyopathy patients during therapy based on hemodynamic electrophysiologic and thallium scintigraphy findings. Abstract. Circulation 88(suppl I):I-209, 1993
161. Gilligan DM, Nihoyannopoulos P, Chan WL, et al. Investigation of a hemodynamic basis for syncope in hypertrophic cardiomyopathy: use of a head-up tilt test. Circulation 85:140, 1992
162. Black IW, Hopkins AP, Lee LCL, et al. Left atrial spontaneous echo contrast: a clinical and echocardiographic analysis. J Am Coll Cardiol 18:398, 1991
163. Leung DYC, Black IW, Cranney GB, et al. Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. J Am Coll Cardiol 24:755, 1994
164. Tsai LM, Chen JH, Fang CJ, et al. Clinical implications of left atrial spontaneous echo contrast in nonrheumatic atrial fibrillation. Am J Cardiol 70:327, 1992
165. Black IW, Chesterman CN, Hopkins AP, et al. Hematologic correlates of left atrial spontaneous echo contrast and thromboembolism in nonvalvular atrial fibrillation. J Am Coll Cardiol 21:451, 1993
166. Fatkin D, Herbert E, Feneley MP. Hematologic correlates of spontaneous echo contrast in patients with atrial fibrillation and implications for thromboembolic risk. Am J Cardiol 73:672, 1994
167. Mahoney C, Ferguson J. The effect of heparin versus citrate on blood echogenicity in vitro: the role of platelet and platelet-neutrophil aggregates. Ultrasound Med Biol 18:851, 1992
168. Kearney K, Mahoney C. Effect of aspirin on spontaneous contrast in the brachial veins of normal subjects. Am J Cardiol 75:924, 1995
169. Karalis DG, Ross JJ, Neri JL. Left ventricular thromboembolism. Circulation 97:498, 1998
170. Tsai L-M, Chen J-H, Tsao C-J. Relation of left atrial spontaneous echo contrast with prethrombotic state in atrial fibrillation associated with systemic hypertension, idiopathic dilated cardiomyopathy, or no identifiable cause (lone). Am J Cardiol 81:1249, 1998
171. Tse H-F, Lau C-P, Cheng G. Relation between mitral regurgitation and platelet activation. J Am Coll Cardiol 30:1813, 1997
172. Kalaria VG, Passannante MR, Shah T, et al. Effect of

mitral regurgitation on left ventricular thrombus formation in dilated cardiomyopathy. Am Heart J 135:215, 1998
172a. Marian AJ, Roberts R. Recent advances in the molecular genetics of hypertrophic cardiomyopathy. Circulation 92;1336, 1995
173. Mann DL, Kent RL, Parsons B, et al. Adrenergic effects on the biology of the adult mammalian cardiocyte. Circulation 85:790, 1992
174. Cohn JN. Plasma norepinephrine and mortality. Clin Cardiol 18(Suppl I): I-9, 1995
175. Mancia G. Sympathetic activation in congestive heart failure. Eur Heart J 11(Suppl A):3, 1990
176. Gilligan DM, Chan WL, Stewart R, et al. Cardiac responses assessed by echocardiograph to changes in preload in hypertrophic cardiomyopathy. Am J Cardiol 73:312, 1994
176a. Vasko MR, Cartwright DB, Knochel JP, et al. Furosemide absorption altered in decompensated congestive heart failure. Ann Intern Med 102:314, 1985
176b. Küpper AJ, Fintelman H, Huige MC, et al. Crossover comparison of the fixed combination of hydrochlorothiazide and triamterene and the free combination of furosemide and triamterene in the maintenance treatment of congestive heart failure. Eur J Pharmacol 30:342, 1986
176c. Ellison DH. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. Ann Intern Med 114:886, 1991
177. Tilley LP, Weitz J. Pharmacologic and other forms of medical therapy in feline cardiac disease. Vet Clin North Am 7:415, 1977
178. Fox PR. Evidence for and against beta-blockers and aspirin for management of feline cardiomyopathies. Vet Clin North Am 21:1011, 1991
179. Bright J, Golden L. Evidence for or against the efficacy of calcium channel blockers for management of hypertrophic cardiomyopathy in cats. Vet Clin North Am 21:1023, 1991
180. Fox PR. Therapy for feline myocardial diseases. *In* Bonagura JD (ed): Kirk's Current Veterinary Therapy. Vol XIII. Philadelphia, WB Saunders (in press)
181. Collucci WS. Molecular and cellular mechanisms of myocardial failure. Am J Cardiol 80:15L, 1997
182. Bigger JT. Why patients with congestive heart failure die: arrhythmias and sudden cardiac death. Circulation 75(Suppl IV):IV28, 1987
183. Francis GS, Cohn JN. Heart failure: mechanisms of cardiac and vascular dysfunction and the rationale for pharmacologic intervention. FASEB J 4:3068, 1990
184. Eaton GM, Cody RL, Nunziata E, et al. Early left ventricular dysfunction elicits activation of sympathetic drive and attenuation of parasympathetic tone in the paced canine model of congestive heart failure. Circulation 92:555, 1995
185. Newton GE, Parker JD. Acute effects of β_1-selective and nonselective β-adrenergic receptor blockade on cardiac sympathetic activity in congestive heart failure. Circulation 94:353, 1996
186. Thompson DS, Naqvi N, Juul SM, et al. Effects of propranolol on myocardial oxygen consumption, substrate extraction, and haemodynamics in hypertrophic obstructive cardiomyopathy. Br Heart J 44:488, 1980
187. Harrison DC, Braunwald E, Glick G, et al. Effects of beta-adrenergic blockade on the circulation, with particular reference to observations in patients with hypertrophic subaortic stenosis. Circulation 29:84, 1964
188. Clarkson PBM, Wheeldon NM, Macleod C, et al. Systolic and diastolic effects of beta-adrenergic stimulation in normal humans. Am J Cardiol 75:206, 1997
189. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. J Am Med Assoc 270:1589, 1993
190. Kennedy HL, Brooks MM, Barker AH, et al. Beta-blocker therapy in the Cardiac Arrhythmia Suppression Trial. Am J Cardiol 74:674, 1994
191. Hjalmarson A. Effects of beta blockade on sudden cardiac death during acute myocardial infarction and the postinfarction period. Am J Cardiol 80(9B):35J, 1997
192. Cody RJ. The sympathetic nervous system and the renin-angiotensin-aldosterone system in cardiovascular disease. Am J Cardiol 80:9J, 1997
193. Heidenreich PA, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. J Am Coll Cardiol 30:27, 1997
194. Muir WW. Clinical pharmacodynamics of beta-adrenoceptor blocking drugs in veterinary medicine. Compend Contin Educ Pract Vet 6:156, 1989
195. Frishman WH. β-Adrenergic blockers. Med Clin North Am 72:37, 1988
196. Quiñones M, Dyer DC, Ware WA, et al. Pharmacokinetics of atenolol in clinically normal cats. Am J Vet Res 57:1050, 1996
196a. Henry PD. Comparative pharmacology of calcium antagonists: nifedipine, verapamil, and diltiazem. Am J Cardiol 46:1047, 1980
196b. Walsh RA. The effects of calcium-entry blockade on left ventricular systolic and diastolic function. Circulation 75(suppl V): V43, 1997
197. Rosing DR, Idän Ipään-Heikkilä U, Maron BJ, et al. Use of calcium-channel blocking drugs in hypertrophic cardiomyopathy. Am J Cardiol 55:Suppl:185B, 1985
198. Bonow RO, Rosing DR, Bacharach SL, et al. Effects of verapamil on left ventricular systolic function and diastolic filling in patients with hypertrophic cardiomyopathy. Circulation 64:787, 1981
199. Hess OM, Grimm J, Krayenbuehl HP. Diastolic function in hypertrophic cardiomyopathy: effects of propranolol and verapamil on diastolic stiffness. Eur Heart J 4:Suppl F:47, 1983
200. Udelson JE, Bonow RO, O'Gara PT, et al. Verapamil prevents silent myocardial perfusion abnormalities during exercise in asymptomatic patients with hypertrophic cardiomyopathy. Circulation 79:1052, 1989
200a. Iwase M, Sotobata I, Takagi S, et al. Effects of diltiazem on left ventricular diastolic behavior in patients with hypertrophic cardiomyopathy: evaluation with exercise pulsed Doppler echocardiography. J Am Coll Cardiol 2:143, 1987
201. Suwa M, Hiroto Y, Kawamura K. Improvement in left ventricular diastolic function during intravenous and oral diltiazem therapy in patients with hypertrophic cardiomyopathy: an echocardiographic study. Am J Cardiol 54:1047, 1984
201a. Betocchi S, Piscione F, Losi MA, et al. Effects of diltiazem on left ventricular systolic and diastolic function in hypertrophic cardiomyopathy. Am J Cardiol 78:451, 1996
202. Natarajan D, Sharma SC, Sharma VP. Pulmonary edema with diltiazem in hypertrophic obstructive cardiomyopathy. Am Heart J 120:229, 1990
203. Johnson LM, Atkins CE, Keene BW, et al. Pharmacokinetic and pharmacodynamic properties of conventional and CD-formulated diltiazem in cats. J Vet Intern Med 10:316, 1996

204. Hager WD, Davis BR, Riba A, et al. Absence of a deleterious effect of calcium channel blockers in patients with left ventricular dysfunction after myocardial infarction: the SAVE study experience. Am Heart J 135:406, 1998
205. Ishikawa K, Nakai S, Takenaka T, et al. Short-acting nifedipine and diltiazem do not reduce the incidence of cardiac events in patients with healed myocardial infarction. Circulation 95:2368, 1997
206. Messerli FH, Michalewicz L. Safety of heart rate-lowering calcium antagonists: lessons from controlled trials. Am Heart J 134 (Suppl):S21, 1997
207. ACC/AHA guidelines for the management of patients with acute myocardial infarction. J Am Coll Cardiol 78:153, 1996
208. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 20:248, 1992
209. Chatterjee K. Heart failure therapy in evolution. Circulation 94:2689, 1996
210. Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 316:1429, 1987
211. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 325:293, 1991
212. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 327:685, 1992
213. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 342:821, 1993
214. IMPROVE Study Group. Acute and short-term hemodynamic, echocardiographic, and clinical effects of enalapril maleate in dogs with naturally acquired heart failure: results of the Invasive Multicenter PROspective Veterinary Evaluation of Enalapril study. J Vet Intern Med 9:234, 1995
215. COVE Study Group. Controlled clinical evaluation of enalapril in dogs with heart failure: results of the Cooperative Veterinary Enalapril Study Group. J Vet Intern Med 9:243, 1995
216. Sharpe DN, Coxon RJ, Douglas JE, et al. Low-dose captopril in chronic heart failure: acute haemodynamic effects and long-term treatment. Lancet 2:1154, 1980
217. Maslowski AH, Nicholis MG, Ikram H, et al. Haemodynamic, hormonal, and electrolyte response to captopril in resistant heart failure. Lancet 1:71, 1981
218. Cody RJ, Covit A, Schaer G, et al. Captopril pharmacokinetics and the acute hemodynamic and hormonal response in patients with severe chronic congestive heart failure. Am Heart J 104:1180, 1982
219. Sun Y, Weber KT. Fibrosis and myocardial ACE: possible substrate and independence from circulating angiotensin II. J Cardiac Failure 1:81, 1994
220. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. Circulation 83:1849, 1991
221. Factor SM, Butany J, Sole MK, et al. Pathologic fibrosis and matrix connective tissue in the subaortic myocardium of patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 171:1343, 1991
222. Lechin MM, Quiñones MA, Omran A, et al. Angiotensin-I converting enzyme genotypes and left ventricular hypertrophy in patients with hypertrophic cardiomyopathy. Circulation 92:1808, 1995
222a. Hodges RD, Lothrop CD Jr. Atrial natriuretic factor concentration in the cat; Abstract. J Vet Intern Med 5:129, 1991
223. Weber KT. Extracellular matrix remodeling in heart failure; a role for de novo angiotensin II generation. Circulation 96:4065, 1997
224. Vaughn DE, Pfeffer MA. Angiotensin converting enzyme inhibitors and cardiovascular remodeling. Cardiovasc Res 28:159, 1994
225. Dahlof B. Effect of angiotensin II blockade on cardiac hypertrophy and remodeling: a review. J Hum Hypertens 9(Suppl):S37, 1995
226. Haber HL, Powers ER, Gimple LW, et al. Intracoronary angiotensin converting enzyme inhibition improves diastolic function in patients with hypertensive left ventricular hypertrophy. Circulation 89:2616, 1994
227. Sudhir K, Chou TM, Hutchinson SJ, et al. Coronary vasodilation induced by angiotensin-converting enzyme inhibition in vivo: differential contribution of nitric oxide and bradykinin in conductance and resistance arteries. Circulation 93:1734, 1996
227a. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction; systematic overview of individual data from 100,000 patients in randomized trials. Circulation 97:2202, 1998
228. Hartmann A, Puetz A, Hopf R. Effects of long-term ACE-inhibitor therapy in hypertrophic cardiomyopathy (HCM). J Am Coll Cardiol Suppl A:234A, 1995
229. Kyriakidis M, Triposkiadis F, Dernelli J, et al. Effects of cardiac versus circulatory angiotensin-converting enzyme inhibition on left ventricular diastolic function and coronary blood flow in hypertrophic cardiomyopathy. Circulation 97:1342, 1998
230. Sanders N, Hamlin R, Buffington T, et al. Effects of enalapril on healthy cats; Abstract. J Vet Intern Med 6:139, 1992
231. King JN, Humbert-Droz R, Maurer M. Pharmacokinetics of benazepril and inhibition of plasma ACE activity in cats; Abstract. J Vet Intern Med 10:163, 1996
232. Cohn JN, Simon A, Johnson G, VHeFT Study Group. Relationship of plasma norepinephrine and plasma renin activity to mortality in heart failure: V-HeFT II; Abstract. Circulation 84 (Suppl II):II310, 1991
233. Pollick C. Disopyramide in hypertrophic cardiomyopathy: noninvasive assessment after oral administration. Am J Cardiol 62:1252, 1988
234. Rosing DR, Kent KM, Maron BJ, et al. Verapamil therapy: a new approach to the pharmacologic treatment of hypertrophic cardiomyopathy. II. Effects on exercise capacity and symptomatic status. Circulation 60:1208, 1979
235. Angelini A, Calzolari V, Thiene G, et al. Morphologic spectrum of primary restrictive cardiomyopathy. Am J Cardiol 80:1046, 1997
236. Hirota Y, Shimizu G, Kita Y, et al. Spectrum of restrictive cardiomyopathy: report of the national survey in Japan. Am Heart J 120:188, 1990
237. Reisinger J, Dubrey SW, Falk RH. Cardiac amyloidosis. Cardiol Rev 5:317, 1997
238. Lewis AB. Clinical profile and outcome of restrictive cardiomyopathy in children. Am Heart J 123:1589, 1992
239. Fox PR. Restrictive cardiomyopathy. Proc 14th Annu Vet Med Forum, 1996, pp 235–236
240. Bonagura JB, Fox PR. Restrictive cardiomyopathy. *In* Bonagura JD (ed): Kirk's Current Veterinary Therapy. Vol XII. Philadelphia, WB Saunders, 1995, p 863

241. Liu SK, Fox PR. Restrictive cardiomyopathy in the cat; Abstract Lab Invest 68:25A, 1993
241a. Saxon B, Hendrick M, Waddle JR. Restrictive cardiomyopathy in a cat with hypereosinophilic syndrome. Can Vet J 32:367, 1991
242. Stalis IH, Bossbaly MJ, Van Winkle TJ. Feline endomyocarditis and left ventricular endocardial fibrosis. Vet Pathol 32:122, 1995
243. Scott DW, Randolph JF, Walsh KM. Hypereosinophilic syndrome in a cat. Feline Pract 14:22, 1985
244. Pedersen NC, Giffey S, Grahn R, et al. A transmissible myocarditis/diaphragmitis of cats manifested by transient fever and depression. Feline Pract 21:13, 1993
245. McEwen SA, Valli VEO, Hilland TJ. Hypereosinophilic syndrome in cats: a report of three cases. Can J Comp Med 49:248, 1985
246. Zientek DM, King DL, Dewan SJ, et al. Hypereosinophilic syndrome with rapid progression of cardiac involvement and early echocardiographic abnormalities. Am Heart J 130:1295, 1995
247. Arbustini E, Morbini P, Grasso M, et al. Restrictive cardiomyopathy, atrioventricular block and mild to subclinical myopathy in patients with desmin-immunoreactive material deposits. J Am Coll Cardiol 31:645, 1998
248. Gottdiener JS, Maron BJ, Schooley RT, et al. Two-dimensional echocardiographic assessment of the idiopathic hypereosinophilic syndrome: anatomic basis of mitral regurgitation and peripheral embolization. Circulation 67:572, 1983
249. Shabetai R. Controversial issues in restrictive cardiomyopathy. Postgrad Med J 68:S47, 1992
250. Child JS, Perloff JK. The restrictive cardiomyopathies. Cardiol Clin 6:289, 1988
251. Spyrou N, Foale R. Restrictive cardiomyopathies. Curr Opin Cardiol 9:344, 1994.
252. Katritsis D, Wilmshurst PT, Wendon JA, et al. Primary restrictive cardiomyopathy: clinical and pathologic characteristics. J Am Coll Cardiol 18:1230, 1991
253. Fitzpatrick AP, Shapiro LM, Rickards AF, et al. Familial restrictive cardiomyopathy with atrioventricular block and skeletal myopathy. Br Heart J 63:114, 1990
254. Aroney C, Bett N, Radford D. Familial restrictive cardiomyopathy. N Z J Med 18:877, 1988
255. Mady C, Barretto AC, Oliveira SA, et al. Evolution of the endocardial fibrotic process in endomyocardial fibrosis. Am J Cardiol 68:402, 1991
256. Fujioka S, Koide H, Kitaura Y. Molecular detection and differentiation of enteroviruses in endomyocardial biopsies and pericardial effusions from dilated cardiomyopathy and myocarditis. Am Heart J 131:760, 1996
257. Martin A, Webber S, Fricker F, et al. Acute myocarditis: rapid diagnosis by PCR in children. Circulation 90:330, 1994
258. Schowengerdt KO, Ni J, Denfield SW, et al. Association of parvovirus B19 genome in children with myocarditis and cardiac allograft rejection. Circulation 96:3549, 1997
259. Ni J, Bowles N, Kim Y, et al. Viral infection of the myocardium in endocardial fibroelastosis: Molecular evidence for the role of mumps virus as an etiologic agent. Circulation 95:133, 1997
260. Meurs KM, Fox PR, Magnon A, et al. Polymerase chain reaction (PCR) analysis for feline viruses in formalin-fixed cardiomyopathic hearts identifies panleukopenia. Abstract. J Vet Intern Med 12:201, 1998
261. Olinde KD, O'Connell JB. Inflammatory heart disease: pathogenesis, clinical manifestations, treatment of myocarditis. Annu Rev Med 45:481, 1994
262. Kolbeck PC, Steenbergen C, Wolfe JA, et al. The correlation of mononuclear cell phenotype in endomyocardial biopsies with clinical history and cardiac dysfunction. Am J Clin Pathol 91:37, 1989
262a. Brummer DG, Moise NS. Infiltrative cardiomyopathy responsive to chemotherapy in a cat with lymphoma. J Am Vet Med Assoc 195:1116, 1989
263. Fauci AS, Harley JB, Roberts WC, et al. The idiopathic hypereosinophilic syndrome: clinical, pathophysiologic, and therapeutic considerations. Ann Intern Med 97:79, 1982
264. Tai PC, Ackerman SJ, Spry CJ, et al. Deposits of eosinophil granule proteins in cardiac tissues of patients with eosinophilic endomyocardial disease. Lancet 1:643, 1987
265. Schaffer SW, Dimayuga ER, Kayes SG. Development and characterization of a model of eosinophil-mediated cardiomyopathy in rats infected with *Toxocara canis*. Am J Physiol 262:H1428, 1992
266. Liu SK. Cardiovascular pathology. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 625
267. Berger PB, Duffy J, Reeder GS, et al. Restrictive cardiomyopathy associated with the eosinophilia-myalgia syndrome. Mayo Clin Proc 69:162, 1994
268. Pion PD, Kittleson MD, Rogers QR, et al. Myocardial failure in cats associated with low plasma taurine: a reversible cardiomyopathy. Science 237:764, 1987
269. Pion PD, Kittleson MD, Rogers QR, et al. Taurine deficiency myocardial failure in the domestic cat. *In* Pasante-Morales H (ed): Functional Neurochemistry of Taurine. New York, Alan R Liss Inc, 1990, p 423
270. Pion PD, Lewis J, Greene K, et al. Effect of meal-feeding and food deprivation on plasma and whole-blood taurine concentrations in cats. J Nutr 121:S177, 1991
271. Pion PD, Kittleson MD, Lewis J, et al. Taurine deficiency myocardial failure: incidence and relation to tissue taurine concentration; Abstract. J Vet Intern Med 5:123, 1991
272. Sisson DD, Knight DH, Helinski C, et al. Plasma taurine concentrations and M-mode echocardiographic measures in healthy cats and cats with dilated cardiomyopathy. J Vet Intern Med 5:232, 1991
273. Skrodzki M, Trautvetter E, Monch E. Plasma taurine levels in healthy cats and cats with cardiac disorders. J Nutr 121:S171, 1991
274. Pion PD, Kittleson MD, Skiles ML, et al. Dilated cardiomyopathy associated with taurine deficiency in the domestic cat: relationship to diet and myocardial taurine content. *In* Lombardini JB, Schaffer SW, Azuma J (eds): Taurine: New Dimensions on Nutrition and Mechanisms of action. New York, Plenum Press, 1992, p 63
275. Pion PD, Kittleson MD, Thomas WP, et al. Clinical findings in cats with dilated cardiomyopathy and relationship of findings to taurine deficiency. J Am Vet Med Assoc 201:267 1992
276. Pion PD, Kittleson MD, Thomas WP, et al. Response of cats with dilated cardiomyopathy to taurine supplementation. J Am Vet Med Assoc 201:275, 1992
277. Morris JG, Rogers QR. The metabolic basis for the taurine requirement of cats. *In* Lombardini BJ, Schaffer SW, Azuma J (eds). Taurine: New Dimensions on Nutrition and Mechanisms of Action. New York, Plenum Press Inc, 1992
278. Fox PR, Sturman JA. Myocardial taurine concentrations in cats with cardiac disease and in healthy cats fed taurine-modified diets. Am J Vet Res 53:237, 1992
279. Novotny MJ, Hogan PM, Paley DM, et al. Systolic and

diastolic dysfunction of the left ventricle induced by dietary taurine deficiency in cats. Am J Physiol 261:H121, 1991
280. Fox PR, Trautwein EA, Hayes KC, et al. Comparison of taurine, α-tocopherol, retinol, selenium, and total triglycerides and cholesterol concentrations in cats with cardiac disease and in healthy cats. Am J Vet Res 54:563, 1993
281. Skiles ML, Pion PD, Hird DW, et al. Epidemiologic evaluation of taurine deficiency and dilated cardiomyopathy in cats. Abstract. J Vet Intern Med 4:117, 1990
282. Fox PR, Petrie JP, Liu SK, et al. Clinical and pathologic features of cardiomyopathy characterized by myocardial failure in 49 cats: 1990–1995. Abstract. J Vet Intern Med 11:139, 1997
283. Lawler DF, Templeton AJ, Monti KL. Evidence for genetic involvement in feline dilated cardiomyopathy. J Vet Intern Med 7:383, 1993
284. Grünig E, Tasman JA, Kücherer H, et al. Frequency and phenotypes of familial dilated cardiomyopathy. J Am Coll Cardiol 31:186, 1998
285. Baig MK, Goldman JH, Caforio ALP, et al. Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. J Am Coll Cardiol 31:195, 1998
286. Martino TA, Liu P, Sole MJ. Viral infection and the pathogenesis of dilated cardiomyopathy. Circ Res 74:182, 1994
287. Rose NR, Neumann DA, Herskowitz A. Coxsackievirus myocarditis. Adv Intern Med 37:411, 1992
288. Latham RD, Mulrow JP, Virmani R, et al. Recently diagnosed idiopathic dilated cardiomyopathy: incidence of myocarditis and efficacy of prednisone therapy. Am Heart J 117:876, 1989
289. Dec GW, Fuster V. Medical progress: idiopathic dilated cardiomyopathy. N Engl J Med 331:1564, 1994
290. Neumann DA. Autoimmunity and idiopathic dilated cardiomyopathy. Mayo Clin Proc 69:193, 1994
291. Grossman W, McLaurin LP, Rolett EL. Alterations in left ventricular relaxation and diastolic compliance in congestive cardiomyopathy. Cardiovasc Res 13:514, 1979
292. Lord PF. Left ventricular diastolic stiffness in dogs with congestive cardiomyopathy and volume overload. Am J Vet Res 37:953, 1976
293. Inoue T, Sakai Y, Morooka S, et al. Coronary flow reserve in patients with dilated cardiomyopathy. Am Heart J 125:93, 1993
294. Dow SW, Fettman MJ, Smith KR, et al. Taurine depletion and cardiovascular disease in adult cats fed a potassium-depleted acidified diet. Am J Vet Res 53:402, 1992
295. Ballèvre O, Piguet-Welsh C, Staempfli A, et al. Taurine kinetics in cats fed processed diets. Vet Int 1:17, 1993
296. Morris JG, Rogers QR, Kim SW, et al. Dietary taurine requirement of cats is determined by microbial degradation of taurine in the gut. Vet Clin Nutr 1:118, 1994
297. Huxtable RJ, Sebring LA. Cardiovascular actions of taurine. *In* Kuriyama K, Huxtable RJ, Iwata H (eds): Sulfur Amino Acids: Biochemical and Clinical Aspects. New York, Alan R. Liss Inc, 1983, p 5
298. Sturman JA. Nutritional taurine and central nervous system development. Ann NY Acad Sci 477:196, 1986
299. Hayes KC. A review of the biological function of taurine. Nutr Rev 34:161, 1976
300. Rabin B, Nicolosi RJ, Hayes KC. Dietary influences on bile acid conjugation in the cat. J Nutr 106:1241, 1976
301. Knopf K, Sturman JA, Armstrong M, et al. Taurine: an essential nutrient for the cat. J Nutr 108:773, 1978
302. Sturman JA. Taurine in development. Physiol Rev 73:119, 1993
303. Wen GY, Sturman JA, Wisniewski HM, et al. Tapetum disorganization in taurine-depleted cats. Invest Ophthalmol Visual Sci 18:1201, 1979
304. Trautwein EA, Hayes KC. Gender and dietary amino acid supplementation influence the plasma and whole blood taurine status of taurine depleted cats. J Nutr 121:3170, 1991
305. Trautwein EA, Hayes KC. Taurine concentrations in human plasma and whole blood: estimation of error from intra- and inter-individual variation and sampling technique. Am J Clin Nutr 52:758, 1990
306. Brest AN. Clinical pharmacology of diuretic drugs. Cardiovasc Clin 14:31, 1984
307. Sonnenblick EH. Force-velocity relations in mammalian heart muscle. Am J Physiol 202:931, 1962
308. Dyke SE, Urschel CW, Sonnenblick EH, et al. Detection of latent function in acutely ischemic myocardium in dogs: comparison of pharmacologic inotropic stimulation and post extrasystolic potentiation (PESP). Circ Res 36:490, 1975
309. Spann JF Jr, Covell JW, Eckberg DL, et al. Contractile performance of the hypertrophied and chronically failing cat ventricle. Am J Physiol 223:1150, 1972
310. Colucci WS, Wright RF, Braunwald E. New positive inotropic agents in the treatment of congestive heart failure. Mechanisms of action and recent clinical developments (first of two parts). N Engl J Med 314:290, 1986
311. Colucci WS, Wright RF, Braunwald E. New positive inotropic agents in treatment of congestive heart failure. Mechanisms of action and recent clinical developments (second of two parts) N Engl J Med 314:349, 1986
312. Kenakin TP. An in vitro quantitative analysis of the alpha adrenoceptor partial agonist activity of dobutamine and its relevance to inotropic selectivity. J Pharmacol Exp Ther 216:210, 1981
313. Ruffolo RR Jr, Spradlin TA, Pollock GD, et al: Alpha and beta adrenergic effects of the stereoisomers of dobutamine J Pharmacol Exp Ther 219:447, 1981
314. Shoemaker WC, Appel PL, Kram HB, et al. Comparison of hemodynamic and oxygen transport properties of dopamine and dobutamine in critically ill surgical patients. Chest 96:120, 1989
315. Maskin CS, Le Jemtel MD, Sonnenblick EH. Inotropic drugs for treatment of the failing heart. Cardiovasc Clin 14:1, 1984
316. Kittleson MD: Dobutamine. J Am Vet Med Assoc 177:642, 1980
317. Tuttle RR, Mills J. Dobutamine: development of a new catecholamine to selectively increase cardiac contractility. Circ Res 36:185, 1975
318. McDonald RH Jr, Goldberg LI, McNay JL, et al. Effects of dopamine in man: augmentation of sodium excretion, glomerular filtration rate, and renal plasma flow. J Clin Invest 43:1116, 1964
319. Goldberg LI. Cardiovascular and renal actions of dopamine: potential clinical implications. Pharmacol Rev 24:1, 1972
320. Chidsey CA, Sonnenblick EH, Morrow AG, et al. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. Am J Med 39:442, 1965
321. van de Borne P, Oren R, Somers VK. Dopamine depresses minute ventilation in patients with heart failure. Circulation 98:126, 1998
322. Beregovich J, Bianchi C, Rubler S, et al. Dose-related hemodynamic and renal effects of dopamine in congestive heart failure. Am Heart J 87:550, 1974

323. Goldberg LI. Dopamine—clinical uses of endogenous catecholamine. N Engl J Med 291:707, 1984
324. Johnson RL. Low-dose dopamine and oxygen transport by the lung. Circulation 98:97, 1998
325. Tewksbury DA. Angiotensin: biochemisty and molecular biology. *In* Laragh JH, Brenner BM (eds): Hypertension: Pathophysiology, Diagnosis, and Management. New York, Raven Press, 1990, p 1197
326. Regitz-Zagrosek V, Leuchs B, Krulls-Munch J, et al. Angiotensin-converting enzyme inhibitors and β-blockers in long-term treatment of dilated cardiomyopathy. Am Heart J 129:754, 1995
327. Sabbah HN, Shimoyama H, Kono T, et al. Effects of long-term monotherapy with enalapril, metoprolol, and digoxin on the progression of left ventricular dysfunction and dilation in dogs with reduced ejection fraction. Circulation 89:2852, 1994
328. Atkins CE, Snyder PS, Keene BW, et al. Efficacy of digoxin for treatment of cats with DCM. J Am Vet Med Assoc 196:1463, 1990
329. Gheorghiade M, Ferguson D. Digoxin: a neurohormonal modulator in heart failure? Circulation 84:2181, 1991
330. Utetsky BF, Young JB, Shahidi FE, et al. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED Trial. J Am Coll Cardiol 22:955, 1993
331. Ferguson DW, Berg WJ, Sanders JS, et al. Sympathoinhibitory responses to digitalis glycosides in heart failure patients. Circulation 80:65, 1989
332. Tsutamoto T, Wada A, Maeda K, et al. Digitalis increases brain natriuretic peptide in patients with severe congestive heart failure. Am Heart J 134:910, 1997
333. Smith ML, Kinugawa T, Dibner-Dunlap ME. Reflex control of sympathetic activity during ventricular tachycardia in dogs. Circulation 93:1022, 1966
334. Erichsen DF, Harris SG, Upson DW. Therapeutic and toxic plasma concentrations of digoxin in the cat. Am Anim Hosp Assoc 14:734, 1978
335. Erichsen DF, Harris SG, Upson DW. Plasma levels of digoxin in the cat: some clinical applications. J Am Anim Hosp Assoc 14:734:1994, 1982
336. Bolton GR, Powell AA. Plasma kinetics of digoxin in the cat. Am J Vet Res 43:1994, 1982
337. Snyder PS, Atkins CE, Keene BW. The effect of aspirin, furosemide and commercial low salt diet on digoxin kinetics in normal cats; Abstract. Proc Fifth Annu Vet Med Forum, ACVIM, 1987, p 922
338. Andersson B, Hamm C, Persson S, et al. Improved exercise hemodynamic status in dilated cardiomyopathy after beta-adrenergic blockade treatment. J Am Coll Cardiol 23:1397, 1994
339. Eichhorn EJ, Heesch CM, Barnett JH, et al. Effect of metoprolol on myocardial function and energetics in patients with nonischemic dilated cardiomyopathy: a randomized, double-blinded, placebo-controlled study. J Am Coll Cardiol 24:1310, 1994
340. Waagstien F. Adrenergic beta-blocking agents in congestive heart failure due to idiopathic dilated cardiomyopathy. Eur Heart J 16 (Suppl O):128, 1996
341. Regitz-Zagrosek V, Leuchs B, Krulls-Munch J, et al. Angiotensin-converting enzyme inhibitors and β-blockers in long-term treatment of dilated cardiomyopathy. Am Heart J 129:754, 1995
342. Asseman P, McFadden E, Bauchart JJ, et al. Why do beta-blockers help in idiopathic dilated cardiomyopathy-frequency mismatch? Lancet 344:803, 1994
343. Sato H, Hori M, Ozaki H, et al. Exercise-induced upward shift of diastolic left ventricular pressure-volume relation in patients with dilated cardiomyopathy. Effects of beta-adrenergic blockade. Circulation 88:2215, 1993
344. Ishida S, Makino N, Masumoto K, et al. Effect of metoprolol on the beta-adrenoceptor density of lymphocytes in patients with dilated cardiomyopathy. Am Heart J 125:1311, 1993
345. Lee TH, Hamilton MA, Stevenson LW, et al. Impact of left ventricular cavity size on survival in advanced heart failure. Am J Cardiol 72:672, 1993
346. Vasan RS, Larson MG, Benjamin EJ, et al. Left ventricular dilatation and the risk of congestive heart failure in people without myocardial infarction. N Engl J Med 336:1350, 1997
347. Moller JH, Lucas RV, Adams P, et al. Endocardial fibroelastosis: a clinical and anatomic study of 47 patients with emphasis on its relationship to mitral insufficiency. Circulation 30:759, 1964
348. Carceller AM, Maroto E, Fouron JC. Dilated and contracted forms of primary endocardial fibroelastosis: a single fetal disease with two stages of development. Br Heart J 63:311, 1990
349. Harpster NK. Cardiovascular diseases of the domestic cat. Adv Vet Sci Comp Med 21:39, 1977
350. van der Linde–Sipman JS, van den Ingh TSGAM, Koeman JP. Congenital heart abnormalities in the cat: a description of sixteen cases. Zentralbl Veterinarmed A 20:419, 1973
351. Paasch LH. The comparative pathology of endocardial fibroelastosis in Burmese cats. PhD dissertation, George Washington University, 1979
352. Paasch LH, Zook BC. The pathogenesis of endocardial fibroelastosis in Burmese cats. Lab Invest 42:197, 1980
353. Zook BC, Chandra RS, Casey HW. The comparative pathology of endocardial fibroelastosis in Burmese cats. Virchows Arch[Pathol Anat] 390:211, 1981
354. Eliot TS Jr, Eliot FP, Lushbaugh CC, et al. First report of the occurrence of neonatal endocardial fibroelastosis in cats and dogs. J Am Vet Med Assoc 133:271, 1958
355. McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J 71:215, 1994
356. Giles TD. New WHO/ISFC Classification of a task not completed; Letter. Circulation 96;2081, 1996
357. Frank R, Fontaine G, Vedel J, et al. Electrocardiologie de quatre cas de dysplasie ventriculaire droite arythmogene. Arch Mal Coeur Vaiss 71:963, 1978
358. Thiene G, Basso C, Nava A. About the histology of arrhythmogenic right ventricular dysplasia; Letter. Circulation 96:2089, 1997
359. Fontaine G, Fontaliran F, Frank R. Arrhythmogenic right ventricular cardiomyopathies; clinical forms and main differential diagnoses. Circulation 97:1532, 1998
360. Gerlis LM, Schmidt-Ott SC, Ho SY, et al. Dysplastic conditions of the right ventricular myocardium: Uhl's anomaly versus arrhythmogenic right ventricular dysplasia. Br Heart J 69:142, 1993
361. Burke AP, Farb A, Tashko G, et al. Arrhythmogenic right ventricular cardiomyopathy and fatty replacement of the right ventricular myocardium. Are they different? Circulation 97:1571, 1998
362. Corrado D, Basso C, Thiene G, et al. Spectrum of clinicopathologic manifestations of arrhythmogenic

right ventricular cardiomyopathy/dysplasia: a multicenter study. J Am Coll Cardiol 30:1512, 1997
363. Basso C, Thiene G, Corrado D, et al. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? Circulation 94:983, 1996
364. Fox PR, Maron BJ, Basso C, et al. Spontaneous occurrence of arrhythmogenic right ventricular cardiomyopathy in the domestic cat: a new animal model of human disease. Circulation 98(Suppl):297 (Abstr), 1998
365. Fontaine G, Fontaliran F, Rosas Andrade F, et al. The arrhythmogenic right ventricle: dysplasia versus cardiomyopathy. Heart Vessels 10:227, 1995
366. Pinamonti B, Sinagra G, Salvi A, et al. Left ventricular involvement in right ventricular dysplasia. Am Heart J 123:711, 1992
367. Mallat Z, Tedgui A, Fontaliran F, et al. Evidence of apoptosis in arrhythmogenic right ventricular dysplasia. N Engl J Med 335:1190, 1996
368. James TN, Nichols MM, Sapire DW, et al. Complete heart block and fatal right ventricular failure in an infant. Circulation 93:1588, 1996
369. Rakover C, Rossi L, Fontaine G, et al. Familial arrhythmogenic right ventricular disease. Am J Cardiol 58:377, 1986
370. Nava A, Scognamiglio R, Thiene G, et al. A polymorphic form of familial arrhythmogenic right ventricular dysplasia. Am J Cardiol 59:1405, 1987
371. Nava A, Thiene G,Canciani B, et al. Familial occurrence of right ventricular dysplasia: a study involving nine families. J Am Coll Cardiol 12:1222, 1988
372. Canciani B, Nava A, Toso V, et al. A casual spontaneous mutation as possible cause of the familial form of arrhythmogenic right ventricular cardiomyopathy (arrhythmogenic right ventricular dysplasia). Clin Cardiol 15:217, 1992
373. Dungan NT, Garson A Jr, Gillette PC. Arrhythmogenic right ventricular dysplasia: a cause of ventricular tachycardia in children with apparent normal hearts. Am Heart J 102:745, 1981
374. Brembilla-Perrot B, Jacquemin L, Houplon P, et al. Increased atrial vulnerability in arrhythmogenic right ventricular disease. Am Heart J 135:748, 1998
375. Peterson ME, Taylor RS, Greco DS, et al. Acromegaly in 14 cats. J Vet Intern Med 4:192, 1990
376. Morrison SA, Randolph J, Lothrop CD Jr. Hypersomatotropism and insulin-resistant diabetes mellitus in a cat. J Am Vet Med Assoc 194:91, 1989
377. Tilley LP, Bond B, Patnaik A, et al. Cardiovascular tumors in the cat. J Am Anim Hosp Assoc 17:1009, 1981
377a. Patnaik AK, Liu SK. Angiosarcomas in cats. J Small Anim Pract 18:191, 1977
378. Mauldin GN, Matus RE, Patnaik AK, et al. Efficacy and toxicity of doxorubicin and cyclophosphamide used in the treatment of selected malignant tumors in cats. J Vet Intern Med 2:60, 1988
379. Page RL, Keene BW. Doxorubicin cardiomyopathy. *In* Kirk RW, Bonagura JD (eds): Kirk's Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1992, p 783
380. O'Keefe DA, Sisson DD, Gelberg HB, et al. Systemic toxicity associated with doxorubicin administration in cats. J Vet Intern Med 7:309, 1993
381. Liu SK. Myocarditis and cardiomyopathy in the dog and cat. Heart Vessels 1 (Suppl 1):122, 1985
382. Liu SK. Myocarditis and cardiomyopathy in the dog and cat. *In* Sekiguchi M, Olsen EGJ, Goodwin JF (eds): Myocarditis and Related Disorders. Tokyo, Springer-Verlag, 1985, p 122
383. Dubey JP, Johnstone I. Fatal neonatal toxoplasmosis in cats. J Am Anim Hosp Assoc 18:461, 1982
384. Yamaguchi RA, Pipers FS, Gamble DA. Echocardiographic evaluation of a cat with bacterial vegetative endocarditis, J Am Vet Med Assoc 183:118, 1983
385. Shousse CL, Meier H. Acute vegetative endocarditis in the dog and cat. J Am Vet Med Assoc 129:278, 1956
386. Tilley LP, Liu SK. Persistent atrial standstill in the dog and cat. Abstract. Sci Proc Am Coll Vet Intern Med, 1983, p 43
387. Carpenter JL, Hoffman EP, Ramanul FC, et al. Feline muscular dystrophy with dystrophin deficiency. Am J pathol 135:909, 1989
388. Haskins ME, Aguirre GD, Jezyk PF, et al. Mucopolysaccharidosis in a domestic short-haired cat: a disease distinct from that seen in the Siamese cat. J Am Vet Med Assoc 175:384, 1979
389. Haskins ME, Aguirre GD, Jezyk PF, et al. The pathology of feline arylsulfatase B deficient mucopolysaccharidosis. Am J Pathol 101:657, 1980
390. Liu SK, Tilley LP, Tashijian RJ. Lesions of the conduction system in the cat with cardiomyopathy. Recent Adv Card Struct Metab 10:681, 1975
391. Collet P. Thrombose de l'aorte posterieur chez un chat. Bull Soc Sci Vet Lyon 33:136, 1930
392. Liu SK, Hsu FS, Lee RCT. An Atlas of Cardiovascular Pathology. Taiwan, Republic of China, Pig Res Inst Taiwan, Wonder Enterprise Co, Ltd, 1989, p 311
393. Waller BF. Anatomic basis of cardiac emboli: a morphologic review. *In* Daniel WG, Kronzon I, Mügge A (eds): Cardiogenic Embolism. Baltimore, Williams & Wilkins, 1996, p 7
394. Pion PD, Kittleson MD. Therapy for feline aortic thromboembolism. *In* Kirk RW (ed): Kirk's Current Veterinary Therapy. Vol X. Philadelphia, WB Saunders, 1989, p 295
395. Flanders JA. Feline aortic thromboembolism. Comp Contin Educ 8:473, 1986
396. Laste NJ, Harpster NK. A retrospective study of 100 cases of feline distal aortic thromboembolism: 1977–1993. J Am Anim Hosp Assoc 31:492, 1995
397. Tilley LP, Liu SK. Cardiomyopathy and thromboembolism in the cat. Feline Pract 5:32, 1975
398. Liu SK, Tilley LP, Lord PF. Feline cardiomyopathy. Recent Adv Card Struct Metab 10:627, 1975
399. Furster V, Chesbro JH. Antithrombotic therapy: role of platelet-inhibitor drugs. I. Current concepts of thrombogenesis: role of platelets (first of three parts). Mayo Clin Proc 56:102, 1981
400. Hirsch J. Hypercoagulability. Semin Hematol 14:409, 1977
401. Edwards WD. Aneurysms and mural thrombi of the left ventricle. Mayo Clin Proc 56:129, 1981
402. Virchow R. Neuer fall von todlicher. Embolie der lungenarterien. Arch Pathol Anat 10:225, 1856
403. Badminon L, Badminon JJ, Turitto VT, et al. Platelet thrombus formation on collagen type I. A model of deep vessel injury—influence of blood rheology, von Willebrand factor and blood coagulation. Circulation 78:1431, 1988
404. Drake TA, Morrissey JH, Edgington TS. Selective cellular expression of tissue factor in human tissues: implication of hemostasis and thrombosis. Am J Pathol 134:1087, 1989
405. Fatkin D, Kelly R, Feneley MO. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. J Am Coll Cardiol 23:961, 1994

406. Roussell L, Biller J, Hajduczok Z, et al. Ischemic cerebrovascular complications and risk factors in idiopathic hypertrophic subaortic stenosis. Stroke 22:1143, 1991
407. Fox PR. Feline thromboembolism associated with cardiomyopathy. Sci Proc Fifth Annu Vet Med Forum, Am Coll Vet Intern Med, 1987, p 714
408. Fox PR, Dodds WJ. Coagulopathies observed with spontaneous aortic thromboembolism in cardiomyopathic cats, abstract. Sci Proc Am Coll Vet Intern Med, 1982, p 83
409. Weiser MG, Kociba GJ. Platelet concentration and platelet volume distribution in healthy cats. Am J Vet Res 45:518, 1984
410. Helinski CA, Ross JN, Platelet aggregation in feline cardiomyopathy. J Vet intern Med 1:24, 1987
411. Dodds WJ. Platelet function in animals: species specificities. *In* de Gaetano G, Garattini S (eds): Platelets: A Multidisciplinary Approach. New York, Raven Press, 1978, p 45
412. Wells EG, Boudreaux MK, Crager CS, et al. Platelet function and antithrombin, plasminogen, and fibrinolytic activities in cats with heart disease. Am J Vet Res 55:619, 1994
413. Jones MP, Alving BM. Evaluation of the hypercoagulable patient. Intern Med 18:37, 1997
414. Schaub RG, Meyers KM, Sande RD. Serotonin as a factor in depression of collateral blood flow following experimental arterial thrombosis. J Lab Clin Med 90:645, 1977
415. Golino P, Ashton JH, Buja LM, et al. Local platelet activation causes vasoconstriction of large epicardial canine coronary arteries in vivo. Thromboxane A_2 and serotonin are possible mediators. Circulation 79:154, 1989
416. Imhoff RK. Production of aortic occlusion resembling acute aortic embolism syndrome in cats. Nature (Lond) 192:979, 1961
417. Schaub RG,Meyers KM, Sande RD, et al. Inhibition of feline collateral vessel development following experimental thrombotic occlusion. Circ Res 39:736, 1976
418. Grygleski RJ. Prostaglandins, platelets and atherosclerosis. Crit Rev Biochem Mol Biol 7:291, 1980
419. Schaub RG, Gates KA, Roberts RE. Effect of aspirin on collateral blood flow after experimental thrombosis of the feline aorta. Am J Vet Res 43:1647, 1982
420. Griffith IR, Duncan ID. Ischaemic neuromyopathy in cats. Vet Rec 104:518, 1979
421. Buchanan JW, Baker GJ, Hill JD. Aortic embolism in cats: prevalence, surgical treatment and electrocardiography. Vet Rec 79:496, 1966
422. Oblad B. A study of the mechanism of the hemodynamic effects of hydralazine in man. Acta Pharmacol Toxicol 20(Suppl 1):1, 1963
423. Thiagarajan P, Benedict CR. Inhibition of arterial thrombosis by recombinant annexin V in a rabbit carotid artery injury model. Circulation 96:2339, 1997
424. Bevers EM, Comfurius P, Zwaal RF. Mechanisms involved in platelet procoagulant response. Adv Exp Med Biol 344:195, 1994
425. Kaplan AP, Castellino FJ, Collen D, et al. Molecular mechanisms of fibrinolysis in man. Thromb Haemost 39:263, 1978
426. Killingsworth CR, Eyster GE, Adams T, et al. Streptokinase treatment of cats with experimentally induced aortic thrombosis. Am J Vet Res 47: 1351, 1986
427. Sherry S. Tissue plasminogen activator (t-PA). N Engl J Med 313:1014, 1985
428. Pion PD, Kittleson MD. Therapy for feline aortic thromboembolism. *In* Kirk RW (ed): Kirk's Current Veterinary Therapy. Vol X. Philadelphia, WB Saunders, 1989, p 295
429. Rosenberg RD, Lam L. Correlation between structure and function of heparin. Proc Natl Acad Sci USA 76:1218, 1979
430. Goldhaber SZ, Sors H. Treatment of venous thrombus and pulmonary embolism. *In* Fuster V, Verstraete M (eds): Thrombosis in Cardiovascular Disorders. Philadelphia, WB Saunders, 1992, p 465
431. Bell RW. Metabolism of Vitamin K and prothrombin synthesis: anticoagulants and the vitamin K–epoxide cycle. Fed Proc 37:2599, 1978
432. Baty CJ. Warfarin prophylaxis in feline aortic thromboembolism. Sci Proc 11th Annu Vet Med Forum, 1993, p 519
433. Khosropanah S, Dinh T, Ezekowitz MD. Aspirin and anticoagulant therapy. *In* Daniel WG, Kronzon I, Mügge A (eds): Cardiogenic Embolism. Baltimore, Williams & Wilkins, 1996, p 290
434. Roth GJ, Stanford N, Majerus PW. Acetylation of prostaglandin synthesis by aspirin. Proc Natl Acad Sci USA 72:3073, 1975
435. Burch JW, Stanford PW. Inactivation of platelet prostaglandin synthetase by oral aspirin. J Clin Invest 61:314, 1979
436. Majerus PW. Arachidonate metabolism in vascular disorder. J Clin Invest 72:1521, 1983
437. Kyrle PA, Eichier HG, Jager U, et al. Inhibition of prostaglandin and thromboxane A_2 generation by low-dose aspirin at the site of plug formation in man in vivo. Circulation 75:1025, 1987
438. Preston FE, Whipps S, Jackson CA, et al. Inhibition of prostacyclin and platelet thromboxane A_2 after low dose aspirin. N Engl J Med 304:76, 1981
439. Moncada S, Vane JR. Pharmacology and endogenous roles of prostaglandin endoperoxides, thromboxane-A_2 and prostacyclin. Pharmacol Rev 30:293, 1978
440. Allen DG, Johnstone IB, Crane S. Effects of aspirin and propranolol alone and in combination on hemostatic determinants in the healthy cat. Am J Vet Res 46:660, 1985
441. Greene CE. Aspirin and feline platelet aggregation. J Am Vet Med Assoc 188:1820, 1985
442. Yeary RA, Swanson W. Aspirin dosages for the cat. J Am Vet Med Assoc 163:1177, 1973
443. Moncada S, Gryglewski R, Bunting S, et al. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. Nature (Lond) 263:663, 1976
444. Willard MD. Treatment of hyperkalemia. *In* Kirk RW (ed): Kirk's Current Veterinary Therapy, Vol IX. Philadelphia, WB Saunders, 1986, p 94

29

Pericardial Disease and Cardiac Tumors

DAVID SISSON
WILLIAM P. THOMAS

Pericardial disease and cardiac tumors are being recognized with increasing frequency.[1] This is largely attributable to the expanded use of echocardiography. In addition, the rising prevalence of some neoplasms such as right atrial hemangiosarcoma may be contributory, particularly in view of the mounting popularity of certain breeds predisposed to cardiac neoplasia.[2]

Although the clinical signs of pericardial disease can be easily overlooked during perfunctory patient evaluation, a methodical approach to the history and physical examination will usually reveal obvious diagnostic clues. The experienced clinician suspects pericardial disease in any dog or cat with ascites or pleural effusion, particularly when heart sounds are muffled and external jugular veins are distended. Cardiac neoplasia presents a more formidable diagnostic challenge. Tumors involving the heart or pericardium can obstruct blood flow into or out of the heart, impair atrioventricular or semilunar valve function, infiltrate the myocardium, induce arrhythmias, precipitate cardiac tamponade, or be clinically silent for long periods of time.

ANATOMY OF THE PERICARDIUM

The heart is enveloped in a tough outer fibroserous membrane, the *parietal pericardium*; a more delicate inner serous membrane, the *visceral pericardium (epicardium)*; and the interposed *pericardial cavity*. The visceral pericardium, which is tightly adherent to the myocardium, is composed of a single layer of mesothelial cells overlying a thin fibroelastic stroma.[3] This serous membrane reflects back at the heart base to line the inner aspect of the fibrous pericardium. The serous lining of the pericardial cavity is composed of mesothelial cells that are endowed with numerous microvilli and occasional cilia. The surrounding fibrous pericardium is composed of a dense layer of interlaced collagen fibers. This fibrous tissue is continuous with the adventitia of the great vessels at the heart base and with the sternopericardiac ligament that attaches the apex of the pericardium to the ventral aspect of the diaphragm. In this fashion, the heart is anchored within the thorax.

PERICARDIAL FLUID. A small volume of fluid, rich in phospholipids, lubricates the interior surfaces of the pericardial sac. In healthy dogs and cats, the volume of the *liquor pericardii* approximates 0.25 ($\pm$0.15) ml/kg body weight.[4] This small fluid volume is not uniformly distributed in the pericar-

dial space. Rather, it tends to collect at the heart base and in the atrioventricular grooves, with only a thin layer over the ventricular free walls.[4] As a result, intrapericardial pressure in the normal animal may not be uniform over the various chambers of the heart.[5] Pericardial fluid is typically clear, contains low protein concentration (1.7 to 3.5 g/dl), and very few cells. Both these constituents tend to increase with pathologic pericardial fluid accumulations.

VASCULAR SUPPLY. The parietal pericardium derives its blood supply mainly from branches of the internal thoracic artery, the aorta, and musculophrenic arteries.[3, 6] The epicardium is nourished by superficial branches of the coronary arteries. Lymphatic drainage of the pericardial sac occurs by vessels emptying into the pretracheal and cardiac lymph nodes, by vessels traveling cranially and caudally along the phrenic nerves, and by vessels returning to the sternal lymph node.[7, 8] The processes regulating the production and removal of pericardial fluid are poorly understood. Current consensus favors elaboration of pericardial fluid from the visceral pericardium by ultrafiltration and its subsequent removal by lymphatics located in the subepicardium and parietal pericardium.[9] In most circumstances, pericardial effusion results from increased capillary permeability and hemorrhage rather than impaired lymphatic drainage.

INNERVATION. The parietal pericardium is innervated by parasympathetic branches of both vagus nerves, the left recurrent laryngeal nerve, and tributaries of the esophageal plexus. It is also innervated by sympathetic nerve fibers from several different intrathoracic ganglia, including the stellate ganglia. The phrenic nerves, which course over the lateral surfaces of the pericardium and supply motor control of the diaphragm, also contain those nerve fibers that communicate pericardial pain.

FUNCTION OF THE PERICARDIUM

"The function of the pericardium is something of an enigma. Like the vermiform appendix, we can very well do without it, and yet when it becomes diseased it can, because of its strategic position, place a stranglehold around the heart and thus threaten life itself."

RALPH SHABETAI, M.D.[9]

The pericardium, by virtue of its structure and location, protects the heart from adjacent infection or malignancy and prevents dislocation of the heart by fixing it within the thorax. The fluid contents and mesothelial cells lining the pericardial sac reduce friction generated by the beating heart. The pericardium also functions to restrain cardiac filling and enhance diastolic ventricular coupling.[9–11] By these mechanisms, the pericardium prevents cardiac overdistention and helps balance the respective outputs of the right and left ventricles. An intact pericardium protects against cardiac rupture, minimizes tricuspid insufficiency, and prevents myocardial hemorrhage induced by acute right-sided heart volume distention.[9]

The restraining function of the pericardium intimates inherent liabilities in certain disease states. Normally, intrapericardial pressure is zero or negative at low cardiac volumes, and the pericardium exerts little effect on cardiac filling. However, because the pericardium is noncompliant and its reserve volume is small, intrapericardial pressure rises rapidly when the volume of its contents increases (Fig. 29–1).[12] Intrapericardial pressure also increases whenever the intracardiac volume increases suddenly.[13] Increased pericardial pressure reduces the transmural distending pressures of the right and left ventricles, resulting in reduced diastolic filling and decreased cardiac output. Such changes are observed during rapid intravenous infusions of solute or following drug administration that decreases systemic venous capacitance. In these circumstances, the right side of the heart dilates to occupy the reserve volume of the pericardial sac, thereby raising intrapericardial pressure. Experimentally, re-

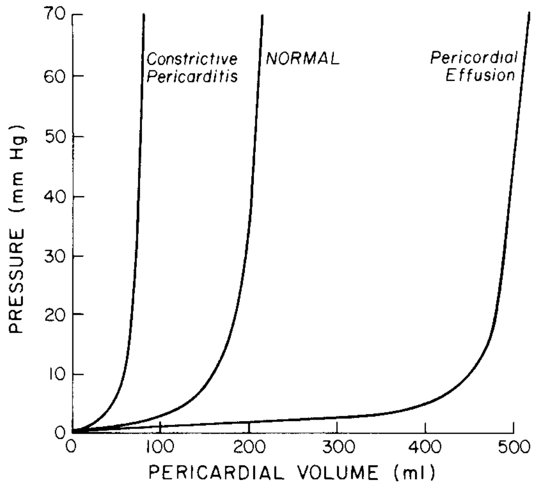


FIGURE 29-1

Idealized pericardial pressure volume curves for normal dogs, dogs with constrictive pericarditis, and dogs with pericardial effusion. Pressure at the ordinate represents pericardial or ventricular diastolic pressure. Each curve has a relatively flat initial portion, followed by a steep portion at pressures above 10 to 15 mm Hg, when the pericardial elastic limit is reached. The volume of pericardial fluid required to produce cardiac tamponade depends on the ability of the pericardium to stretch. When cardiac tamponade is present, removal of a relatively small quantity of fluid can cause rapid reduction in pericardial pressure and, thus, relief of clinical signs. (From Thomas WP. Pericardial disease. *In* Ettinger SJ (ed). Textbook of Veterinary Internal Medicine. 2nd ed. Philadelphia, WB Saunders, 1983, p 1080.)

straint of LV filling by the pericardium is observed when intravenous fluid administration elevates RV end-diastolic pressure above 4 mmHg in dogs.[13] In dogs subjected to acute volume overload, pericardiectomy improves LV filling, increases cardiac output, and aids the redistribution of excess intravascular volume from the pulmonary to the systemic circuit.

The consequences of ventricular interaction and pericardial restraint on LV filling are also apparent when the right side of the heart dilates in response to an acute pressure load. Accordingly, pericardiotomy improves left-sided heart filling and cardiac output in dogs with experimentally induced pulmonary hypertension.[14] Such considerations may have clinical relevance. In a recent study of ten human patients undergoing open heart surgery, closing the pericardium reduced cardiac output by over 20 percent. Reopening the pericardium increased cardiac output and reduced systemic vascular resistance.[15]

The pericardium hypertrophies to accommodate a progressively enlarging heart or gradually increasing volumes of pericardial fluid. This is evident in dogs and cats with progressive cardiomegaly from congenital and acquired heart diseases or with chronic pericardial effusion. Experimentally, excessive pericardial restraint observed in dogs shortly after creation of an arteriovenous fistula is relieved after several weeks due to pericardial growth.[16] However, some human studies of chronic heart failure indicate that exercise capacity may be limited by excessive pericardial restraint.[17]

CONGENITAL PERICARDIAL DISEASES

Congenital pericardial disorders are infrequently encountered in clinical practice. They include peritoneopericardial diaphragmatic hernia, occurring in dogs and cats; intrapericardial cysts, observed only in dogs; and complete absence or partial defects of the pericardium, which are rare in both dogs and cats. Recognition of these lesions is important because they are often amenable to surgical correction.

ABSENCE OF THE PERICARDIUM AND PERICARDIAL DEFECTS

Absence of the entire pericardium is rare in dogs and cats. It does not precipitate clinical signs and is usually detected at necropsy or when thoracic radiographs are obtained for some other reason. Partial pericardial defects (perforations) are only slightly more common, but they engender a small but significant risk of cardiac herniation (Fig. 29–2).[18] Hernia-

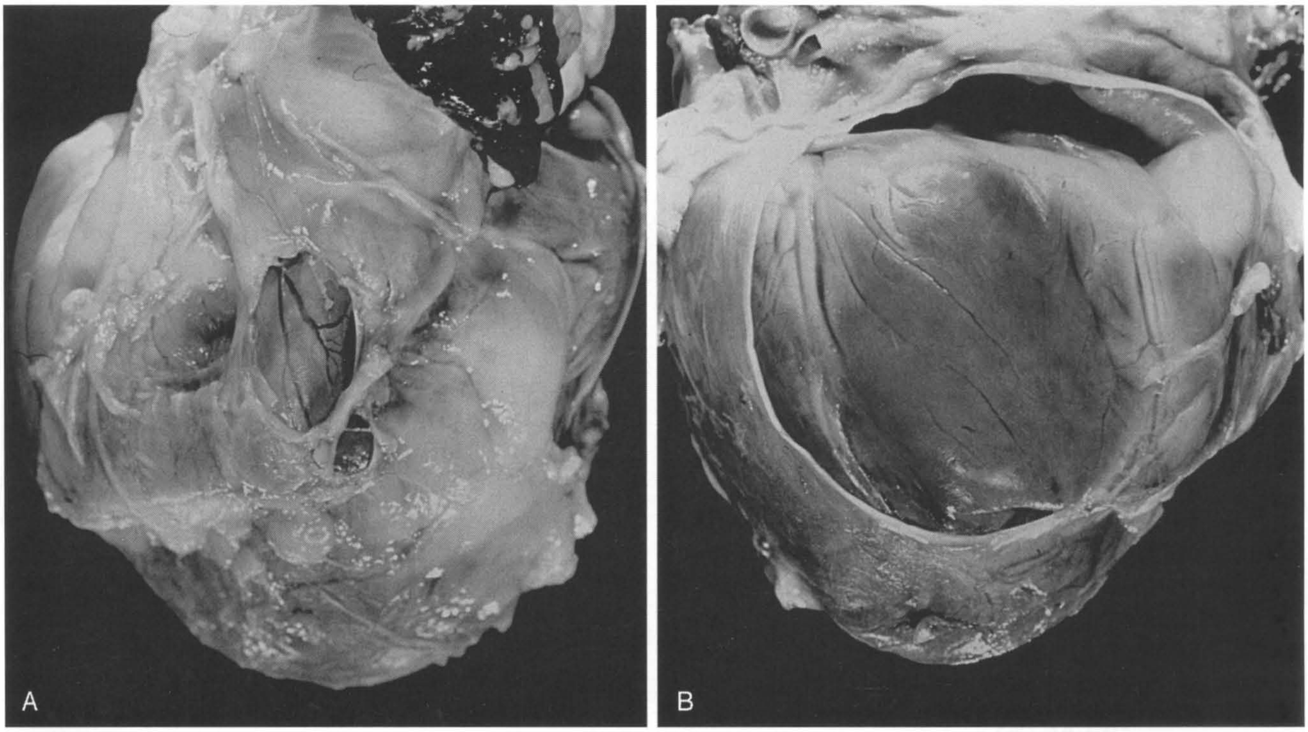


FIGURE 29-2

Congenital pericardial defects. These may represent small (A) or large (B) perforations (holes) in the pericardium. Although usually regarded as incidental findings at necropsy causing no clinical impairment, herniation and entrapment of the heart are possible (see Fig. 29–3).

tion of the left and right atria, right ventricle, and the entire heart has been reported in humans. Single or multiple pericardial defects have been described in nine dogs as incidental necropsy findings.[18, 19] Four dogs had one or more defects (holes) in the left side of the pericardium, three had defects in the right side of the pericardium, and two had defects on both sides. Herniation of the right auricular appendage through a right-sided pericardial defect has been observed by one of the authors (Sisson) in a black Labrador retriever with atrial fibrillation. A calcified thrombus attached to the wall of the herniated right auricle was apparent on thoracic radiographs (Fig. 29–3) and echocardiogram. The atrial appendage containing the thrombus was surgically amputated. Traumatic partial pericardial defects have been reported in other dogs, and several might have been congenital.[20, 21]

PERITONEOPERICARDIAL DIAPHRAGMATIC HERNIA

PREVALENCE. Peritoneopericardial diaphragmatic hernia (PPDH) is the most common congenital pericardial anomaly in dogs and cats,[1] accounting for 0.5 percent of all reported congenital heart defects in dogs (Chapter 23). Its prevalence is probably higher than indicated in this survey because animals with PPDH often do not manifest clinical signs or signs are subtle and missed. According to the Veterinary Medical Data Base at Purdue (January 1993 to May, 1994), PPDH was diagnosed in 0.015 percent of the dogs presented for evaluation and in 0.037 percent of the cats. No sex predilection was apparent for either species. Others have reported that female cats are affected more often than males.[22] About one half of the dogs and one third of the cats that were diagnosed were greater than 4 years of age (Fig. 29–4).

PATHOGENESIS. Congenital PPDH results from faulty development of the dorsolateral septum transversum or from failure of the lateral pleuroperitoneal folds and the ventromedial pars sternalis to unite.[23] It occurs as an isolated defect and in association with umbilical hernias, malformed or absent sternebrae, pectus excavatum, and other congenital heart defects.[24–27] Persian cats and Weimaraners may be predisposed to PPDH.[22, 24] In cats, PPHD may be due to an autosomal recessive gene.[28] Congenital PPDH and multiple cardiac defects were reported in a litter of collies.[24] A related syndrome has been described in a litter of cocker spaniel pups, in which the pericardial space did not communicate with the peritoneal cavity but a portion of the abdominal contents had migrated cranially into a V-shaped, ventrally located, diaphragmatic hernia.[27] Acquired PPDH, sometimes observed in humans following trauma to the diaphragmatic portion of the pericardial sac, is not observed in dogs and cats because this anatomic arrangement is absent.

CLINICAL SIGNS. Clinical signs vary. They depend upon which organs are displaced into the pericardium and the degree to which organ blood supply and function are compromised. The liver is herniated most fre-

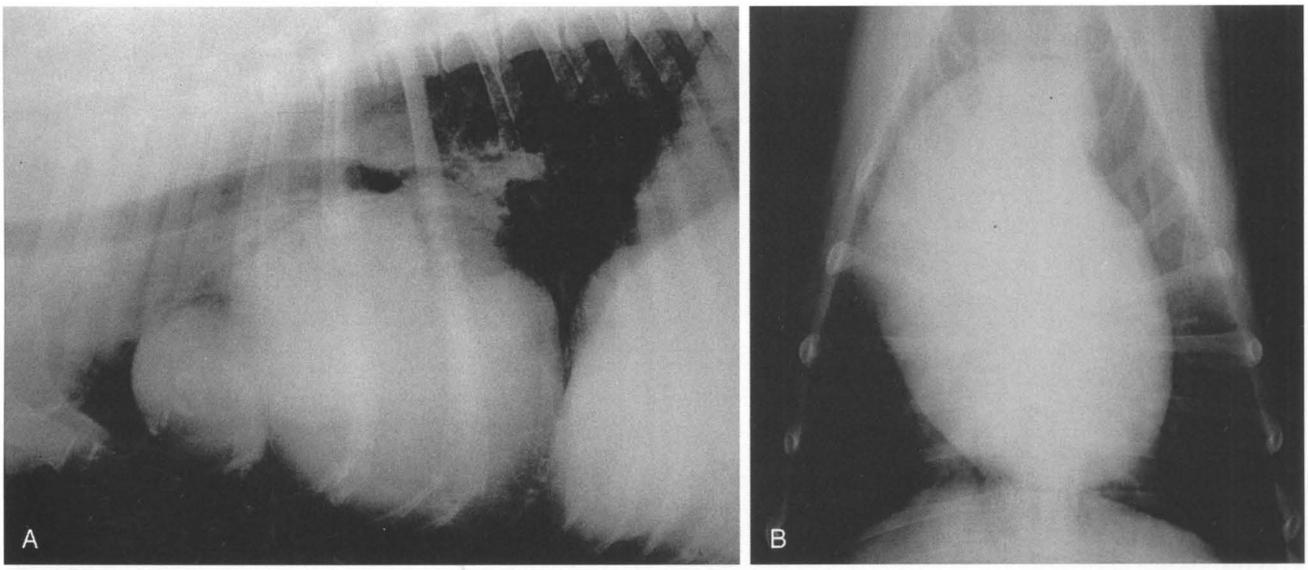


FIGURE 29-3

Lateral (A) and ventrodorsal (B) thoracic radiographs of a dog with a congenital pericardial defect and herniated right auricle. Notice the calcified thrombus visible in the right auricle, which is just cranial to the heart on the lateral radiograph. The diagnosis was confirmed at surgery, and the right auricle was amputated to prevent pulmonary thromboembolism.

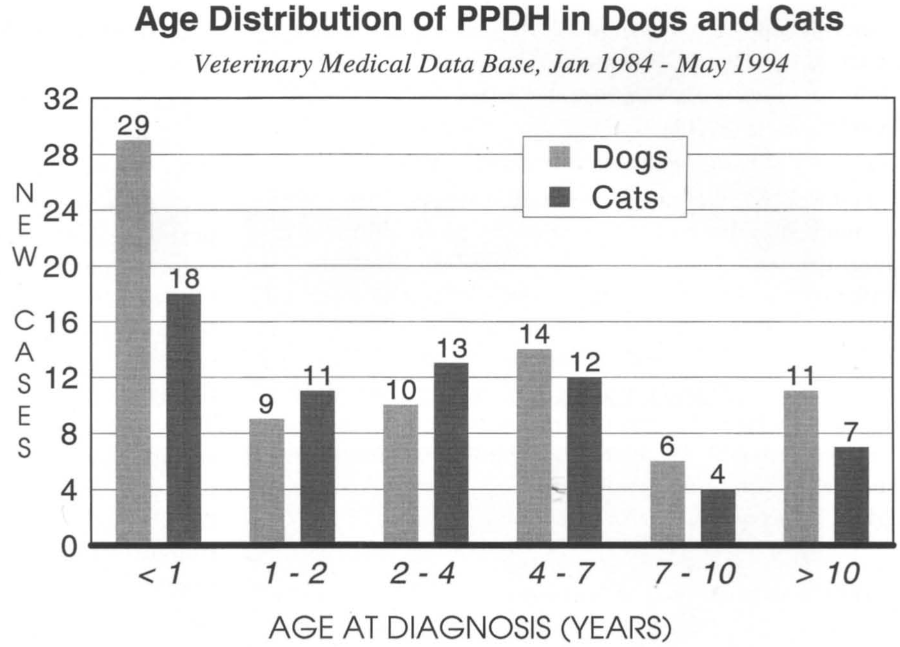


FIGURE 29-4

Age distribution of peritoneopericardial diaphragmatic hernia (PPDH). Many affected animals are asymptomatic for all or part of their lives or are not diagnosed until chest radiographs or an echocardiogram is obtained for some other reason. More than one third of dogs and cats with a PPDH are diagnosed when they are 4 years of age or older.

quently, followed by the small intestine, spleen, and stomach (Fig. 29–5).[22, 23, 26] Thus, vomiting, anorexia, and diarrhea are commonly observed. Respiratory abnormalities, varying from coughing or wheezing to severe dyspnea, are the next most frequently observed clinical signs. Signs of hepatoencephalopathy are occasionally observed due to hepatic incarceration and cirrhosis. Only rarely are heart failure and cardiac tamponade observed.

PHYSICAL EXAMINATION. In many patients the physical examination is unremarkable. In some, the heart sounds are muffled and the cardiac impulse is absent or displaced. Abdominal palpation of animals with large hernias may reveal a lack of normally palpable organs. Some affected animals are emaciated or stunted. The possibility of PPDH should be considered whenever a cranial abdominal hernia is discovered. Frequently PPDH is first suspected when thoracic radiographs are carefully evaluated. Radiographic changes include cardiomegaly, dorsal elevation of the trachea, silhouetting of the cardiac and diaphragmatic borders, the presence of gas-filled stomach or intestine in an intrapericardiac location, and collections of in-

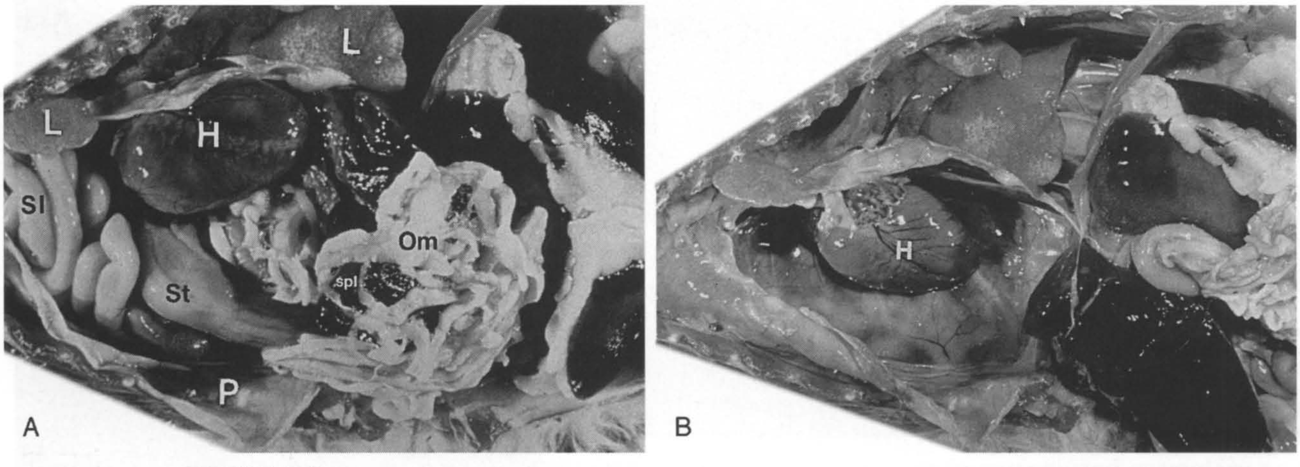


FIGURE 29-5

Clinical signs in dogs and cats with peritoneopericardial diaphragmatic hernia (PPDH) vary in relation to the organs that are displaced into the pericardium. (A) Right lateral view (the left thoracic cage has been removed) of a cat with PPDH in which the stomach *(St)*, small intestine *(SI)*, spleen *(spl)*, omentum *(Om)*, and a portion of the liver herniated into the pericardial sac surrounding the heart (H). L, lungs; P, pericardium. (B) Same view as in (A). The communication between the pericardial sac and the peritoneal cavity can be visualized only after the herniated organs are removed.

trapericardial fat adjacent to the more radiodense heart (Fig. 29–6). Electrocardiographic changes include small amplitude complexes and deviation of the heart's mean electrical axis.

DIAGNOSIS. Herniated segments of intestine and stomach may be easily identified by plain thoracic radiographs or following oral barium administration. Ultrasonography is particularly useful when the spleen or portions of the liver have herniated into the pericardial sac.[29] Liver function should always be assessed prior to surgical intervention. Other useful diagnostic techniques include selective or nonselective angiography, tomography, positive or negative contrast peritoneography, pneumography, magnetic resonance imaging, and computerized axial tomography.

TREATMENT. Surgical reduction of the hernia and repair of the diaphragmatic defect are advisable in many but not all instances of PPDH.[22, 26] Surgical imperatives include herniation of the stomach into the pericardial sac, bowel obstruction, and vascular embarrassment to the liver or other herniated organ. Occasionally, a small PPDH is discovered in an asymptomatic older animal or an animal with signs unrelated to the hernia. Frequently, only the omentum or a small portion of the liver has herniated into the pericardial sac. Observation rather than surgery is often the prudent choice, particularly in older animals with other systemic diseases.

INTRAPERICARDIAL CYSTS

PATHOLOGY AND PATHOGENESIS. These unusual structures have been described in only a few dogs less than 3 years of age;[30, 31] most had one or more large unilocular or multilocular "cystlike" masses within the pericardial sac (Fig. 29–7). Histologically they were cystic hematomas, as they lacked epithelial or endothelial lining cells. In two of these dogs, the cysts were found in association with a PPDH. In the other five dogs, the cyst was invested in a stalk of tissue that was firmly attached to the apex of the parietal pericardium. These findings suggest that intrapericardial cysts develop in most instances as a result of congenital herniation and entrapment of omentum or a portion of the falciform ligament into the pericardial sac. Clusters of thin-walled, fluid-filled cysts, similar to human pericardial coelomic cysts, were discovered within the pericardial sac of a female Lhasa Apso. In humans, pericardial cysts are congenital malformations outside the pericardial sac in the cardiophrenic angle. Such outpouchings may (diverticula) or may not (cysts) communicate with the pericardial space.[32] These have not been identified in dogs or cats.

CLINICAL FINDINGS. Most dogs with intrapericardial cysts are presented with signs of cardiac tamponade (muffled heart sounds, distended jugular veins, ascites, weak arterial pulses, and, less frequently, pleural effusion). Cardiac filling may be compromised by accumu-

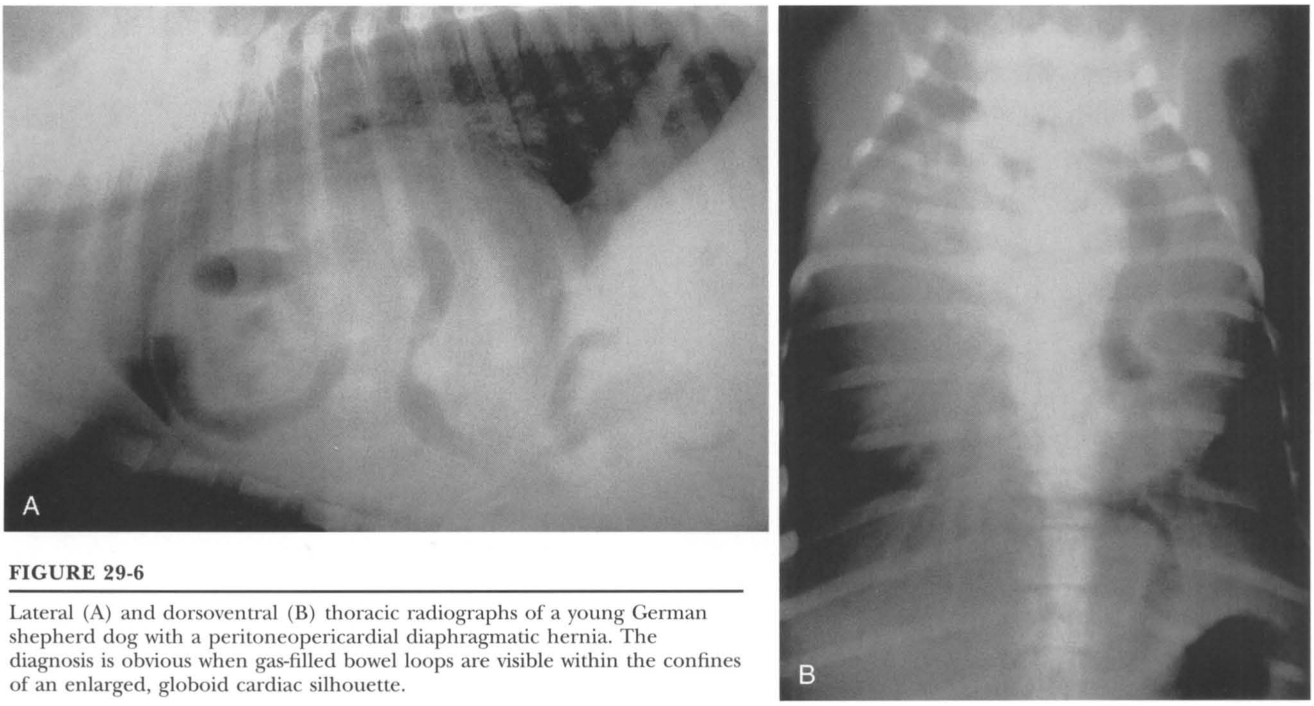


FIGURE 29-6

Lateral (A) and dorsoventral (B) thoracic radiographs of a young German shepherd dog with a peritoneopericardial diaphragmatic hernia. The diagnosis is obvious when gas-filled bowel loops are visible within the confines of an enlarged, globoid cardiac silhouette.

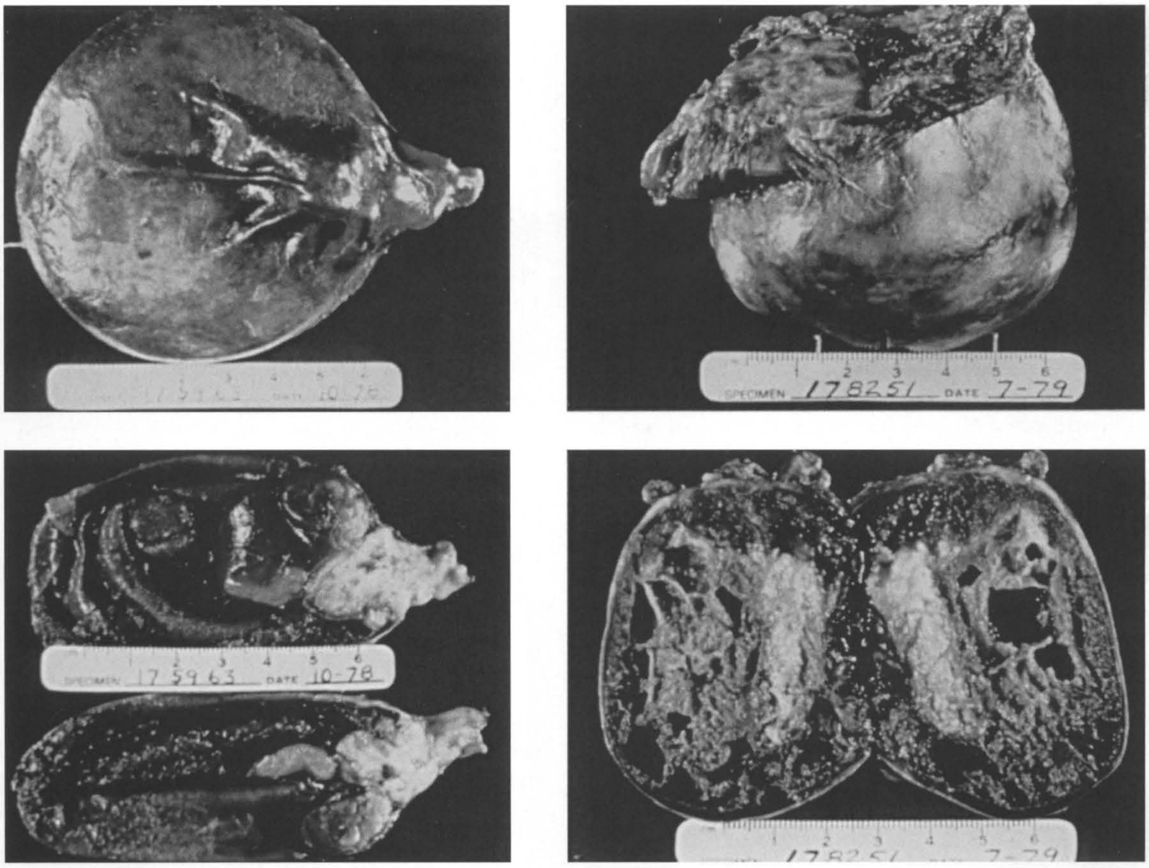


FIGURE 29-7

Unilocular (right) and multilocular (left) pericardial cysts are most likely cystic hematomas that develop in fatty tissue that becomes trapped in a small peritoneopericardial diaphragmatic hernia. Clinical signs are usually manifest prior to 3 years of age. (From Sisson D, Thomas WP, Reed J, et al. Intrapericardial cysts in the dog. J Vet Intern Med 7:364, 1993.)

lation of pericardial fluid (cardiac tamponade) or by direct impingement of the cyst on the right side of the heart (compression). The electrocardiogram typically reveals a change in mean electrical axis and small amplitude QRS complexes. Electrical alternans is absent as the heart is not free to swing in the pericardial space. Thoracic radiographs reveal either a globoid cardiac silhouette or an odd-shaped, enlarged heart shadow with a protuberance on its right caudal aspect (Fig. 29–8*A*,*B*). Intrapericardial cysts are easily demonstrated by two-dimensional echocardiography (Fig. 29–8*C*) or pneumopericardiography. Pericardial effusion is frequently present.

TREATMENT. Cardiac tamponade may be temporarily relieved by percutaneous drainage of either the pericardial fluid or the fluid within the cyst. Surgical exploration of the pericardium and diaphragm is then indicated. Median sternotomy facilitates cyst removal and the identification and repair of any associated PPDH. Cyst removal and subtotal pericardiectomy result in permanent resolution of all clinical signs.

ACQUIRED PERICARDIAL DISEASES

PERICARDIAL EFFUSION AND CARDIAC TAMPONADE

ETIOLOGY. Excess pericardial fluid accumulates with a variety of systemic, cardiac, and pericardial disorders. *Idiopathic pericardial effusion* is the most frequently reported non-neoplastic disorder causing cardiac tamponade in dogs.[33–35] This poorly understood malady is diagnosed most often in middle-aged large and giant-breed dogs. Bacterial pericardial infections are very infrequent but have been reported secondary to migrating foreign bodies, bite wounds, perforation of the thoracic esophagus, and extension of adjacent pulmonary infection.[36–38] Fungal pericarditis is unusual, with the notable exception of *Coccidioides immitis* infections in dogs living in southwestern United States.[39] Left atrial rupture resulting in cardiac tamponade is an

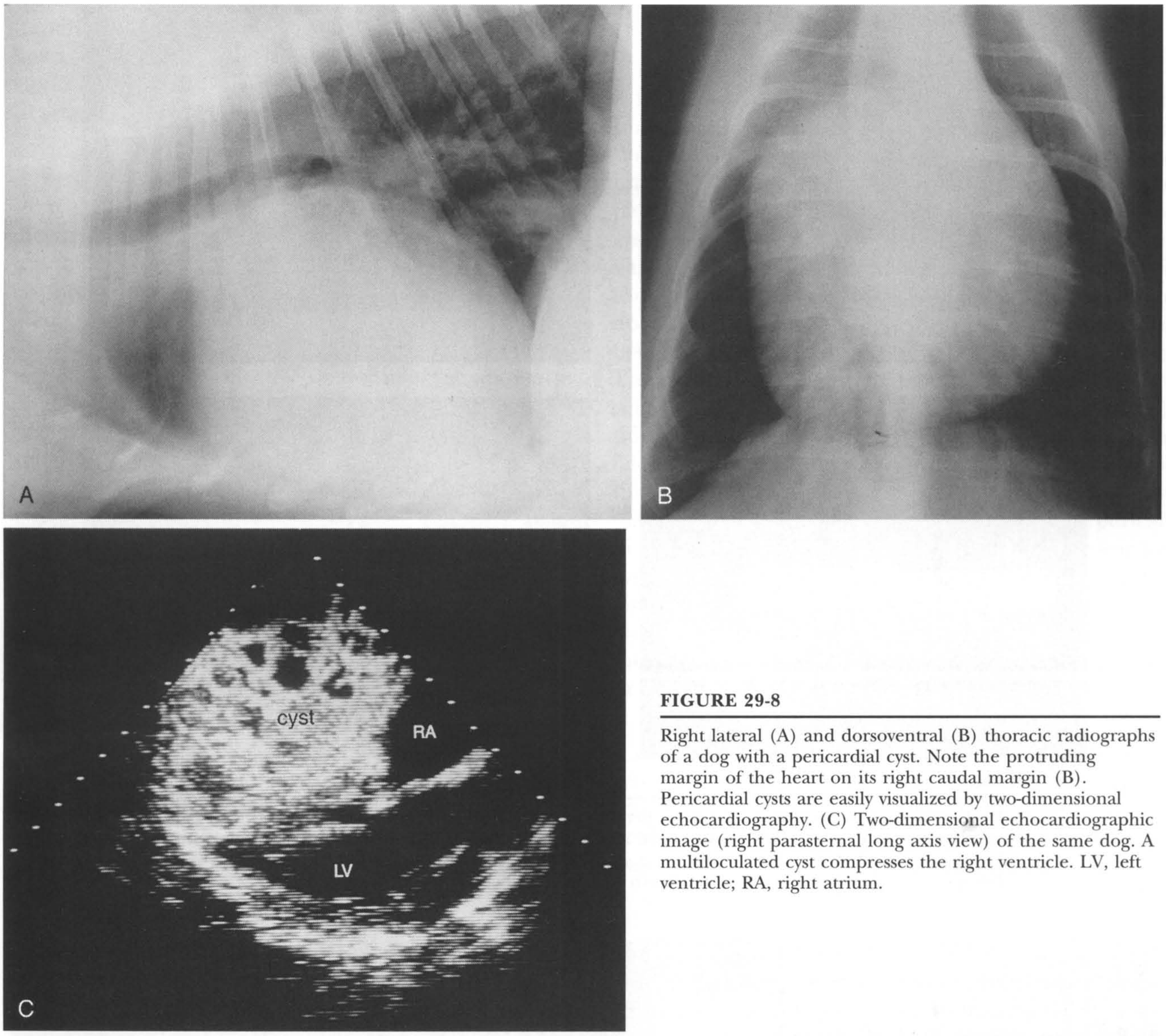


FIGURE 29-8

Right lateral (A) and dorsoventral (B) thoracic radiographs of a dog with a pericardial cyst. Note the protruding margin of the heart on its right caudal margin (B). Pericardial cysts are easily visualized by two-dimensional echocardiography. (C) Two-dimensional echocardiographic image (right parasternal long axis view) of the same dog. A multiloculated cyst compresses the right ventricle. LV, left ventricle; RA, right atrium.

uncommon but well-documented complication of degenerative valvular disease in small-breed dogs.[40] There are several reports of metallic projectiles lodging in the pericardial sac and inducing pericardial effusion.[41, 42] Various cardiac or systemic diseases are associated with small volumes of acellular pericardial fluid, but such effusions rarely cause cardiac tamponade.[19, 39, 43]

DOGS. The most frequently identified cause of pericardial effusion and cardiac tamponade is cardiac neoplasia, most commonly hemangiosarcoma or heart-base tumors (Fig. 29–9).[1, 39, 42–46] The term *heart-base tumor* describes any tumor located at this anatomic site. Most heart-base tumors are chemodectomas, arising from the aortic bodies in the periadventitial tissue of the ascending aorta and base of the pulmonary artery.[47–49] Thyroid, parathyroid, and other tumors are also sometimes located at the heart base.[50, 51] Many other tumors arising from or metastasizing to the heart or pericardium can cause pericardial effusion and cardiac tamponade.[39, 42, 43] Mesothelioma is the most frequently diagnosed primary pericardial neoplasm (Fig. 29–10).[52, 53] It is an important cause of neoplastic pericardial effusion in dogs but is much less common in cats.[54]

CATS. Pericardial effusion is diagnosed much less frequently. Cardiac neoplasia is less prevalent in cats than in dogs, and idiopathic effusive pericarditis is not a recognized clinical syndrome in cats. Some reported causes include feline infectious peritonitis, lymphosarcoma, heart-base tumors, a variety of other malignancies, and cardiomyopathy (Fig. 29–11).[55–57] Most cats with cardiomyopathy have no or only small amounts of pericardial fluid.

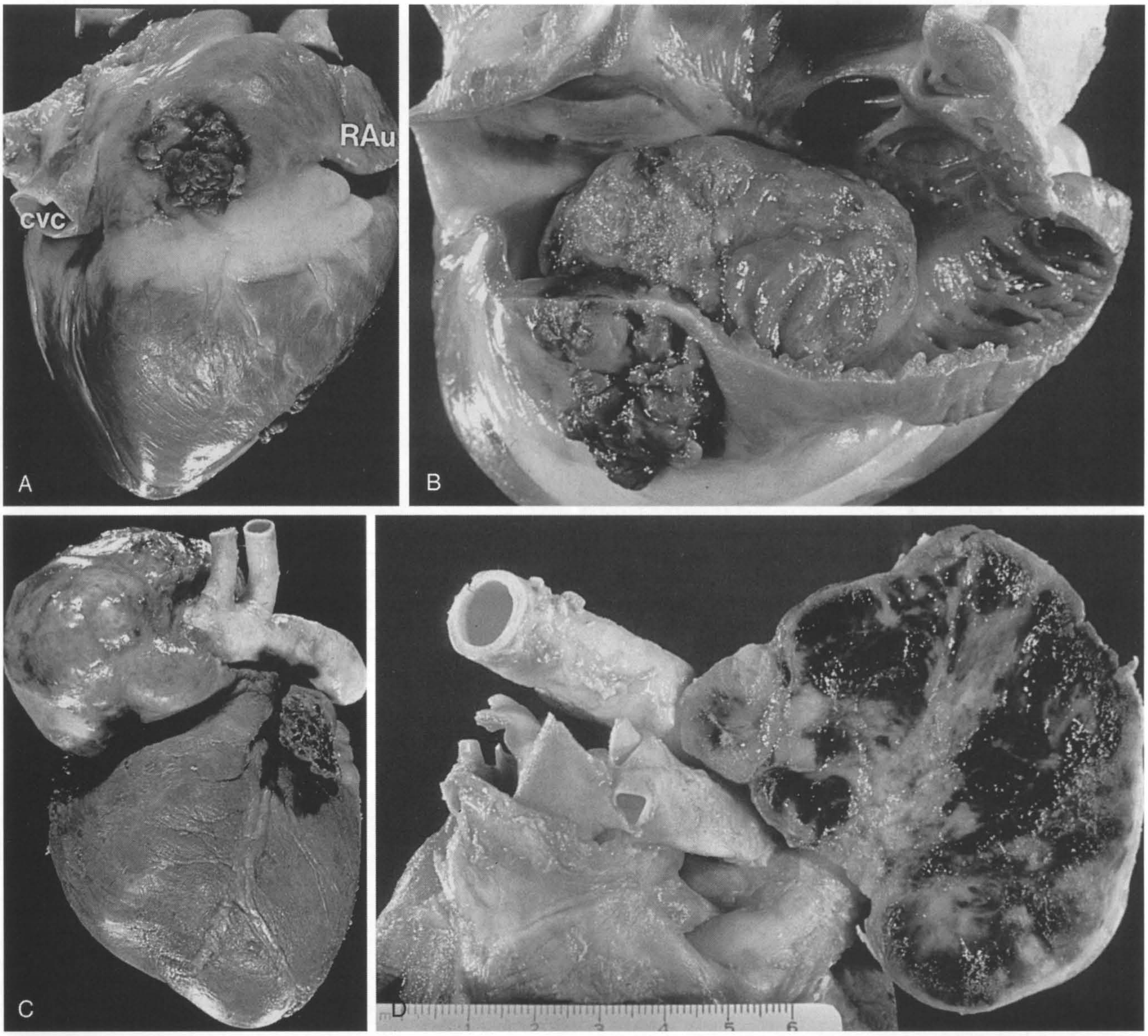


FIGURE 29-9

Two of the most common cardiac tumors in dogs are hemangiosarcoma (*A* and *B*) and heart base tumors (*C* and *D*). Hemangiosarcomas usually involve the right auricle or the right atrium, causing bloody pericardial effusion. (A) Notice the hemangiosarcoma emerging from the epicardium of the right atrium near the atrioventricular junction. Caudal vena cava *(cvc)* and right auricle *(RAu)*. (B) The same heart viewed from the right dorsolateral aspect. The right atrial wall has been dissected away to reveal a large mass obstructing right atrial filling. This view also shows how the tumor metastasized through the endocardium to emerge from the epicardial surface. (C) Canine heart viewed from the left lateral aspect illustrating a heart-base tumor. The most common heart-base tumor is a chemodectoma arising from the aortic bodies in the periadventitial tissue of the aorta. (D) This cross-section through the heart-base tumor shows areas of necrosis and hemorrhage.

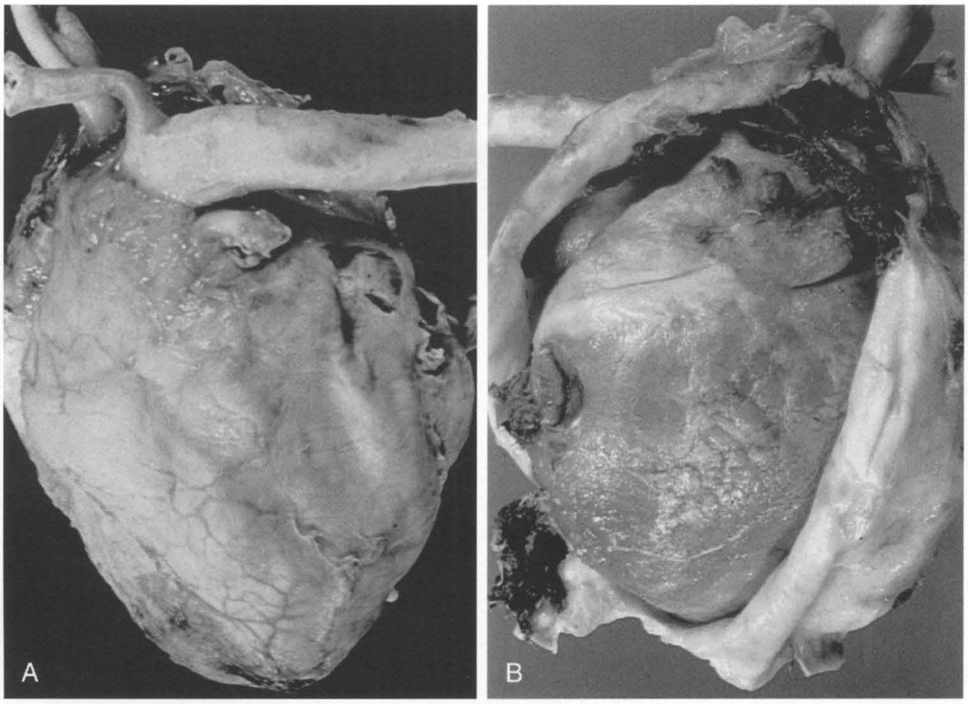


FIGURE 29-10

Pericardial mesotheliomas cause diffuse thickening of the pericardium as seen here, without formation of distinctive, focal, mass lesions. Neither echocardiography nor gross necropsy can easily distinguish clumps of neoplastic mesothelial cells from loose aggregates of fibrin and entrapped red blood cells. (A) Left lateral aspect of a canine heart with pericardial mesothelioma. The pericardium is intact and diffusely thickened. (B) The thickened pericardium has been incised and reflected cranially and caudally to reveal the heart and focal accumulations of neoplastic tissue.

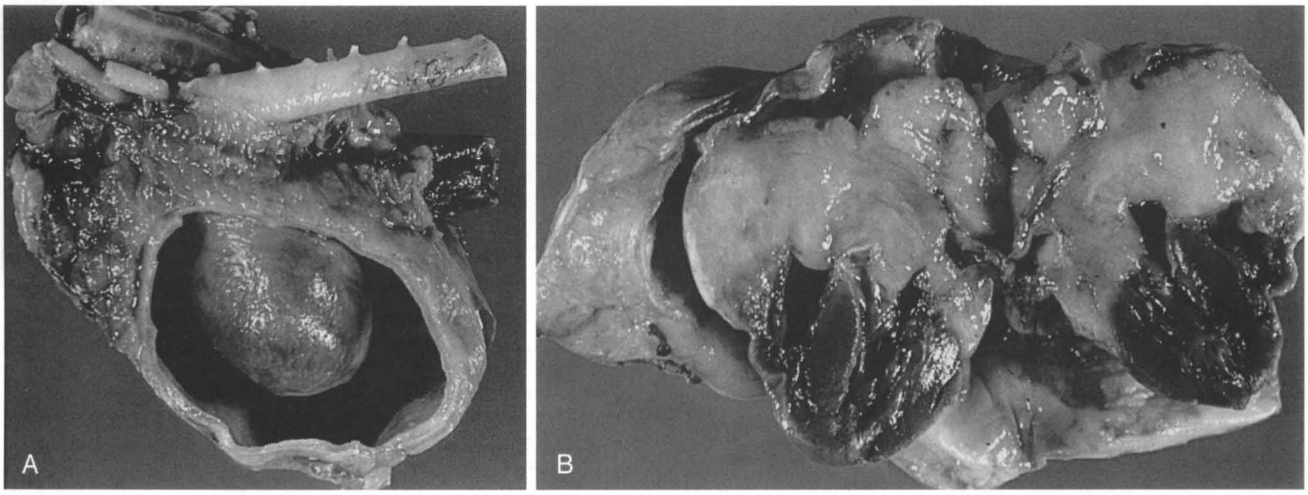


FIGURE 29-11

Feline infectious peritonitis (FIP) and lymphosarcoma are two of the most common causes of pericardial effusion in cats. (A) Gross specimen from a cat that died from FIP infection. The left lateral portion of pericardium has been dissected away to reveal a diffusely thickened pericardium. An enlarged pericardial cavity surrounds the heart within. (B) Longitudinally sectioned heart from a cat (same as in Fig. 29–19) that died from lymphosarcoma. The pericardium, both atria, and heart base are diffusely infiltrated.

PATHOPHYSIOLOGY OF CARDIAC TAMPONADE

HEMODYNAMIC CHANGES. The misconception that cardiac tamponade is an "all-or-none" phenomenon was once advanced[58] under the misconception that pericardial effusion causes no hemodynamic changes so long as intrapericardial pressure is less than right ventricular filling pressure. More correctly, pericardial effusion begins to exert hemodynamic consequences as soon as intrapericardial pressure rises above zero.[59] Moreover, the hemodynamic effects of pericardial effusion occur in a graded fashion as pericardial pressure increases further (Fig. 29–12). Importantly, pulsus paradoxus is not a reliable indicator of the severity of cardiac tamponade.[59]

As pericardial fluid accumulates and intrapericardial pressure rises, the filling pressures of the right and left ventricles also rise. Initially, transmural distending pressure (i.e., intracardiac pressure minus intrapericardial pressure), declines slightly and stroke volume falls modestly in accordance with Starling's law. As intrapericardial pressure rises further, it equilibrates first with RV filling pressure, a state defined as right-sided heart tamponade, and eventually with left heart filling pressure, defined as left heart tamponade (Fig. 29–13). When intrapericardial pressure rises to equal or exceed RV filling pressure, cardiac output is significantly compromised and systemic venous pressure is substantially elevated.

The severity of circulatory compromise is a function of intrapericardial pressure rather than volume of pericardial fluid. When intrapericardial pressure rises slowly, signs of low cardiac output are usually accompanied by physical signs of systemic congestion, such as ascites or pleural effusion. Relatively small effusions that accumulate suddenly (e.g., traumatic hemorrhage, rodenticide toxicity, left atrial tear, or iatrogenic coronary artery laceration) cause profound circulatory embarrassment if intrapericardial pressure rises rapidly; cardiogenic shock develops before signs of systemic congestion are apparent.

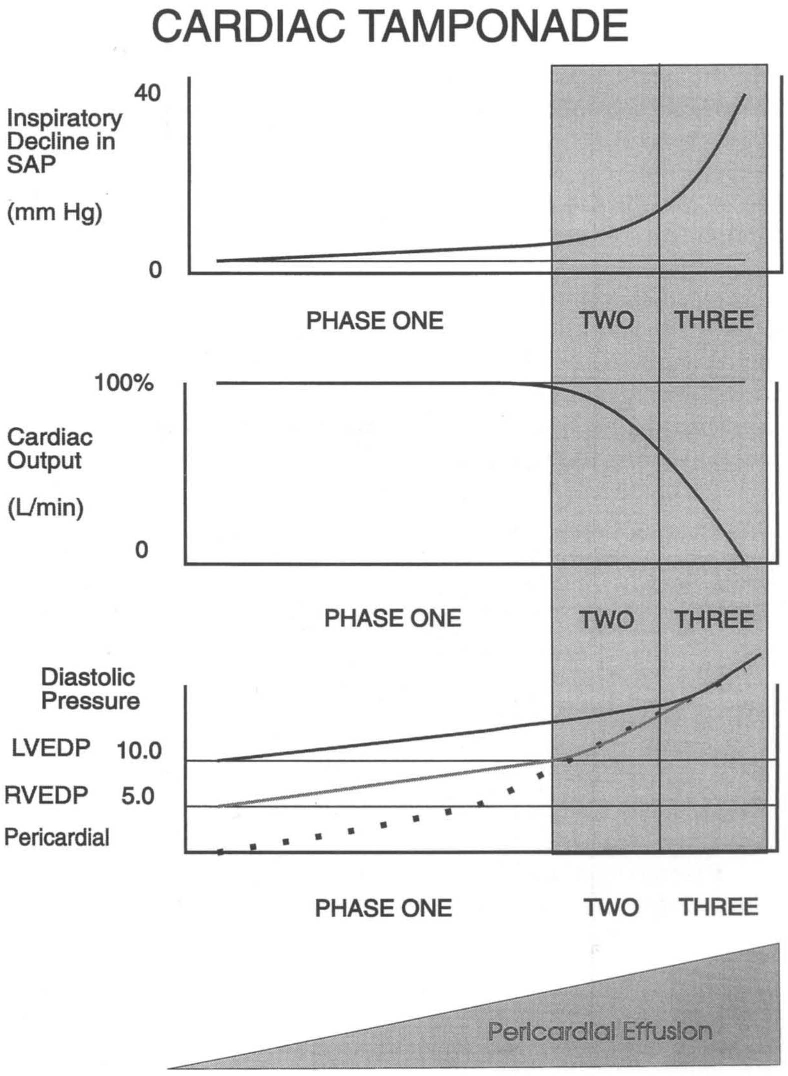


FIGURE 29-12

Cardiac tamponade is a progressive phenomenon. Phase One: Patients are compromised, albeit modestly in this phase, wherein pericardial pressure is elevated but less than right atrial pressure. Phase Two: This constitutes right heart tamponade, defined as that state in which pericardial pressure equals or exceeds right atrial pressure. Exercise intolerance and signs of systemic venous congestion (ascites) are manifested. Phase Three: This is defined as left-sided heart (or biventricular) tamponade, and cardiac output is usually severely compromised. Femoral pulses are weak, and pulsus paradoxus is usually evident. (Modified from Reddy PS, Curtiss El, Uretsky BF. Spectrum of hemodynamic changes in cardiac tamponade. Am J Cardiol 66:1487, 1990. With permission from Excerpta Medica Inc.)

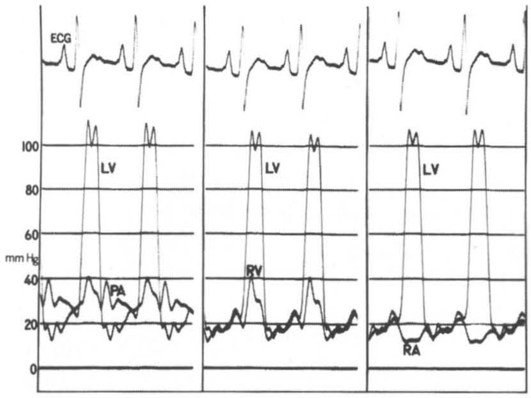


FIGURE 29-13

Intracardiac pressures recorded from a dog with cardiac tamponade due to pericardial effusion. Simultaneous pressures are recorded from the left ventricle *(LV)*, pulmonary artery *(PA)*, right ventricle *(RV)*, and right atrium *(RA)*. Note the elevation (20 to 25 mmHg) and equalization of end-diastolic pressures in these chambers. The PA and RV systolic pressures are mildly elevated (40 mmHg), while the LV systolic pressure is normal (110 mmHg). The early diastolic y descent on the atrial and ventricular pressure tracings is not prominent (compare with Fig. 29–21). (From Thomas WP. Pericardial disease. *In* Ettinger SJ (ed). Textbook of Veterinary Internal Medicine. 2nd ed. Philadelphia, WB Saunders, 1983, p 1080.)

In the healthy animal, ventricular filling is primarily accomplished in early diastole when the ventricles are actively relaxing (Chapters 3, 11). The *y descent* of the atrial pressure tracing reflects the important contribution of ventricular relaxation to cardiac filling. With development of cardiac tamponade, cardiac filling during early diastole is substantially abbreviated.[60] Intrapericardial pressure rises rapidly as the ventricles start to expand, and the atrial pressure tracing shows a markedly diminished y descent. Consequently, venous return during the late diastole becomes increasingly important; blood fills the heart primarily during atrial diastole, during inscription of the *x descent* of the atrial pressure tracing.

VASCULAR AND SYSTEMIC ALTERATIONS. Compensatory mechanisms, such as increased heart rate, sodium and water retention, and venoconstriction, blunt any decline in cardiac output, but they further increase cardiac filling pressures. In contrast to other forms of heart failure, plasma concentrations of atrial natriuretic peptide (ANP) do not rise substantially with cardiac tamponade.[61] The usual stimulus for ANP release, atrial distention, is circumvented because the atria are constrained by pericardial effusion. The failure of rising atrial pressures to elicit a natriuretic response contributes to the rapid increase in plasma volume in animals with pericardial disease.

Increased systemic venous pressure causes jugular distention and fluid transudation from systemic capillary beds. Ascites develops when central venous pressure approaches or exceeds 15 mmHg. Pulmonary edema develops only when severe tamponade raises pulmonary venous pressures above 25 mmHg. More modest venous hypertension increases the rate of pleural fluid production and compromises the absorptive ability of subpleural pulmonary lymphatic vessels. Thus, respiratory distress with chronic pericardial effusion is more often a result of pleural effusion rather than pulmonary edema.

Pulsus paradoxus is defined as a greater than 10 percent fall in inspiratory systolic arterial pressure compared with the expiratory value, or a fall in pressure of greater than 10 mmHg (Fig. 29–14).[62] The term *pulsus paradoxus* is somewhat a misnomer as this phenomenon is simply an exaggeration of the normal tendency for systemic arterial pressure to decline slightly during inspiration. During inspiration, there is a surge of venous return to the right heart as intrathoracic pressure falls below that in the extrathoracic systemic veins. The right side of the heart is constrained by pericardial fluid and fills at the expense of the left side of the heart. This causes left ventricular heart stroke volume to decline. During expiration, LV filling improves and stroke volume increases. Thus, pulsus paradoxus is a striking manifestation of ventricular interdependence. It becomes most evident when pressures in the right and left ventricles equilibrate and the importance of preload is accentuated. When pericardial pressure exceeds LV filling pressure, cardiac output is severely compromised and almost all patients evidence pulsus paradoxus. However, pulsus paradoxus is observed in some patients even when the rise in intrapericardial pressure is modest, that is, less than right ventricular heart filling pressure.

CLINICAL MANIFESTATIONS OF PERICARDIAL EFFUSION

HISTORY AND PHYSICAL EXAMINATION. The clinical manifestations of pericardial effusion depend on the rate

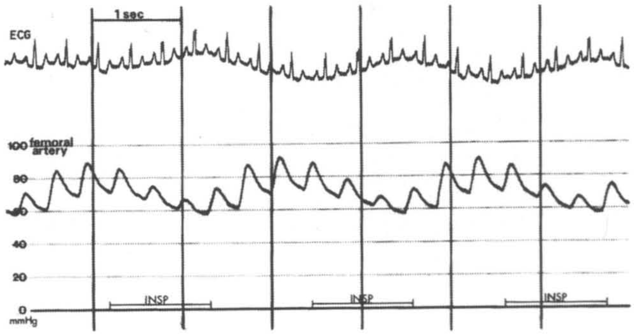


FIGURE 29-14

Direct measurement of femoral artery pressure in a dog with cardiac tamponade reveals pulsus paradoxus. There is an exaggerated fall in mean pressure (> 10 mmHg) and a small pulse pressure during inspiration *(INSP)*. ECG, electrocardiogram. (From Thomas WP. Pericardial disease. *In* Ettinger SJ (ed). Textbook of Veterinary Internal Medicine. 2nd ed. Philadelphia, WB Saunders, 1983, p 1080.)

of rise in intrapericardial pressure. Although acute tamponade may occur, most animals are presented after a chronic course of pericardial effusion with less severe clinical signs. With disseminated neoplasia or systemic infection, clinical signs of the underlying illness often dominate. The presence of a murmur in dogs with pericardial effusion usually indicates the presence of some other disease process. For example, dogs developing a left atrial tear and cardiac tamponade secondary to chronic degenerative valvular disease often have a loud systolic heart murmur, although it is decreased in intensity when compared with previous examinations.

ACUTE PERICARDIAL EFFUSION. Rapidly developing cardiac tamponade causes acute hypotension, cardiogenic shock, rapidly progressive weakness, dyspnea, collapse, or sudden death. Such sequelae are common in dogs with atrial tears, bleeding tumors, and traumatic lacerations of coronary vessels.

CHRONIC PERICARDIAL EFFUSION. The classic triad of abnormalities includes (1) muffled heart sounds, (2) weak arterial pulses, and (3) distended systemic veins. The intensity of the heart sounds is usually diminished, but this finding may be subtle or absent with mild effusion. Large pericardial effusions that accumulate slowly are often well tolerated if intrapericardial pressure remains low owing to pericardial hypertrophy. A vague history of lethargy, weakness, exercise intolerance, and anorexia is common. Chronic elevation of pericardial pressure results in signs of right-sided congestive heart failure such as ascites or pleural effusion. With severe cardiac tamponade, arterial pulse is weak and abrupt from peripheral vasoconstriction and reduced stroke volume. Hypotension may be so profound that the peripheral arterial pulse is difficult to locate. Uncommonly, peripheral vasoconstriction may cause arterial hypertension.[63] Other alterations in pulse quality, such as pulsus paradoxus, are more difficult to detect.

PHYSICAL EXAMINATION FINDINGS. With cardiac tamponade, evidence of impaired venous return and elevated right heart filling pressures are usually present and suggested by jugular venous distention or a positive hepatojugular reflux test. When jugular veins are difficult to inspect, as in obese dogs, measurement of central venous pressure (CVP) will document systemic venous hypertension. The CVP is usually greater than 12 mmHg (normal, $\leq$ 6 mmHg) when cardiac tamponade is present. Hepatomegaly and ascites are evident on physical examination, and more subtle changes can be evaluated by abdominal ultrasonography. Large volumes of pleural effusion alter the effort and pattern of respiration and muffle both the heart and lung sounds. Weight loss occurs commonly in dogs with chronic pericardial effusion from anorexia, chronic hepatic congestion, gastrointestinal protein loss, and cachexia. If these signs are present with a known heart-base or cardiac tumor, thyroid function should be assessed to identify an ectopic functional thyroid tumor.

ELECTROCARDIOGRAPHY. Sinus tachycardia and small amplitude QRS complexes (R < 1 mV in Lead II) are recorded in most dogs and cats with substantial pericardial effusion.[64] Unfortunately, the predictive value of these abnormalities is low, particularly in cats. Other causes of small QRS voltages include hypothyroidism, pleural effusion, obesity, intrathoracic mass lesions, and hypovolemia. Electrical alternans (EA), defined as a beat-to-beat voltage variation of the QRS or ST-T complexes, is more indicative of pericardial effusion (Fig. 29–15). This abnormality may be recorded in up to half of affected dogs but is noted

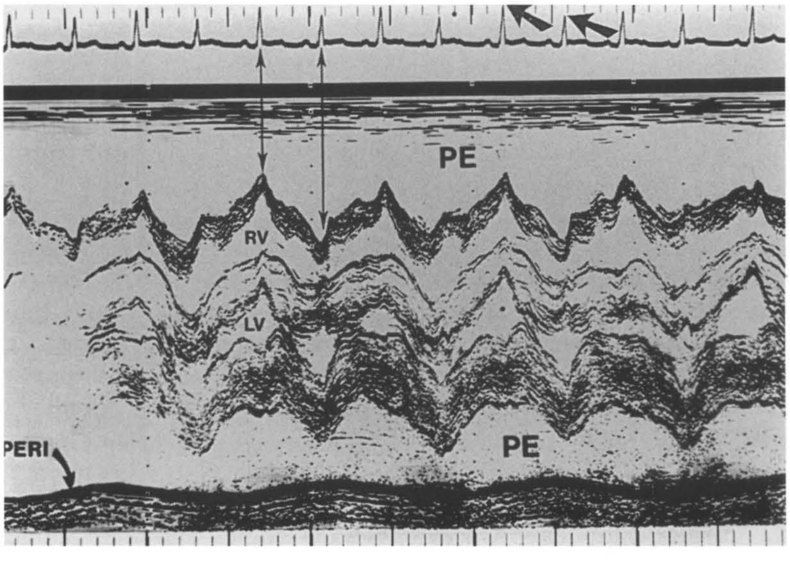


FIGURE 29-15

M-mode echocardiogram and simultaneous ECG from a dog with severe pericardial effusion and electrical alternans. On the ECG, notice how the R wave voltage alternates (electrical alternans) every other beat *(thick arrows)*; this is associated with the heart swinging to and fro within the fluid-filled pericardial sac *(thin arrows)* on the echocardiogram. The ECG also revealed sinus tachycardia and low-voltage QRS complexes. The echo illustrates diastolic collapse of the right ventricle *(RV)*, reduction of the left ventricular dimensions *(LV)*, and a large pericardial effusion *(PE)*, changes compatible with pericardial tamponade. PERI, pericardium.

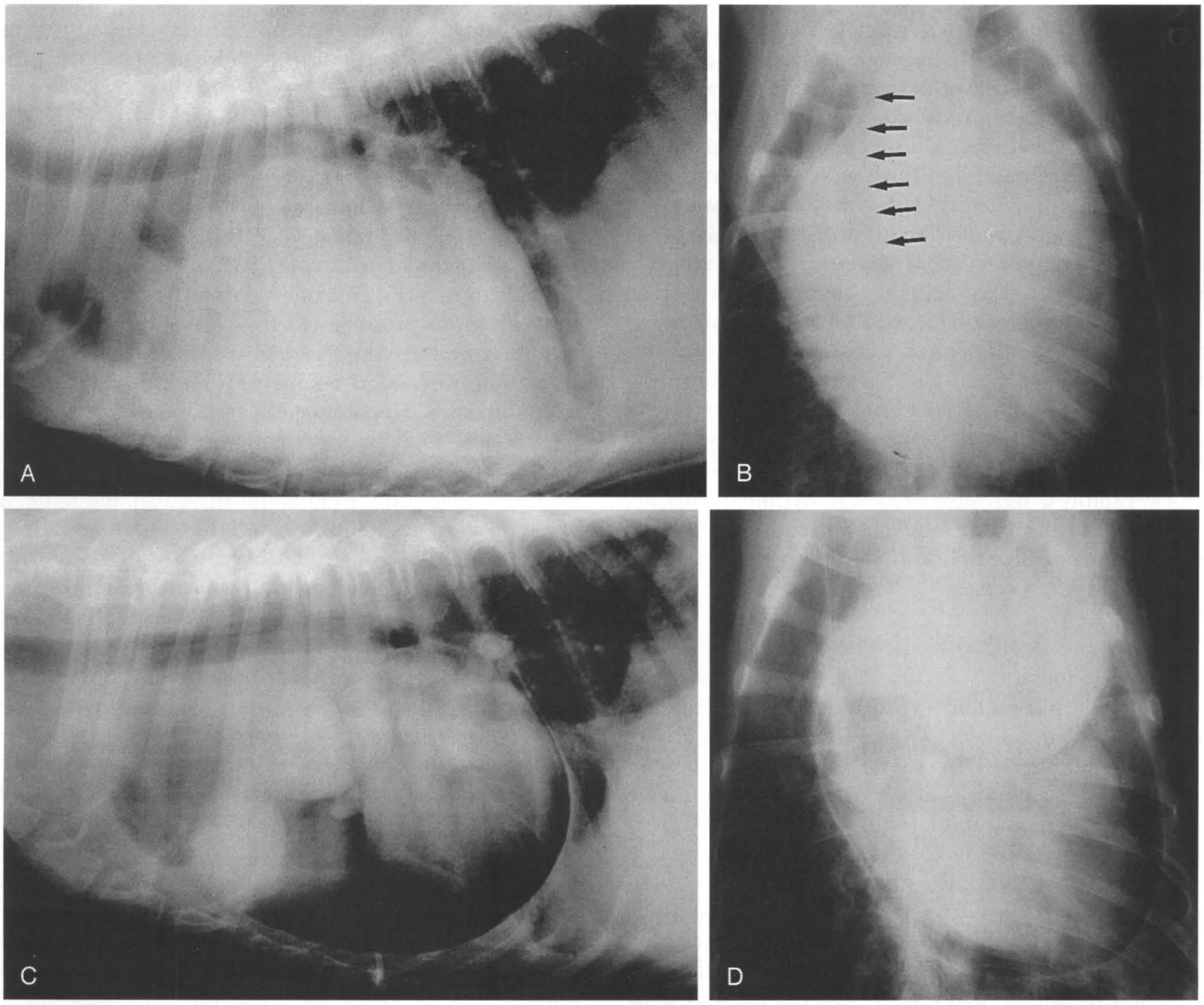


FIGURE 29-16

Tumors of the heart base cause tracheal deviation and may cause pericardial effusion. (A) On the lateral thoracic radiograph, the trachea overlying the cranial portion of the heart is pushed dorsally. (B) On the dorsoventral view, the trachea is displaced rightward *(arrows)*. In both views, the cardiac silhouette is greatly enlarged and generally globoid, obscuring details of specific cardiac chambers. (C, D) In the same dog, the heart base tumor and its relationship to the trachea and heart are clearly illustrated by pneumopericardiography. On the lateral view it is located cranial to the heart; on the dorsoventral view it is evident as a large, circular mass in the left craniolateral quadrant.

less often in cats.[57, 66] Electrical alternans is caused by swinging of the heart within the fluid-filled pericardial sac (Fig. 29–15). A recent study using a nonlinear heart model showed that EA is a rate-dependent phenomenon most likely to occur at heart rates of between 90 and 144 beats per minute.[65] Elevation of the ST segment (indicative of an epicardial injury current) and a variety of ventricular and supraventricular arrhythmias may occur with pericardial effusion. These abnormalities usually resolve following pericardiocentesis.

RADIOGRAPHY. When pericardial fluid accumulates, the cardiac silhouette typically loses its angles and waists and becomes globe-shaped (see Figs. 7–13; 29–16). Distention of the caudal vena cava, hepatomegaly, and ascites are usually evident with chronic effusion and systemic congestion. Enlargement of the pulmonary veins and pulmonary edema is infrequent. Large pleural effusions will obscure many of these changes, and thoracocentesis is often required before the nature of the underlying abnormality is appreciated. Although other cardiac diseases can cause similar radiographic changes, an accurate "radiographic diagnosis" of pericardial effusion can be made by integrating radiographic findings with data from the history and physical examination.

Subtle radiographic clues suggesting the cause of

pericardial effusion are often present. For example, pulmonary metastasis is common with RA hemangiosarcoma and other malignancies involving the heart and pericardium. Multiple thoracic radiographic views should be meticulously evaluated for pulmonary metastasis. Heart-base tumors often cause subtle displacement of the trachea or main stem bronchi. Sternal and hilar lymphadenopathy may be apparent with lymphoma or diffuse neoplasia. Unilateral pleural effusion with pericardial disease often signifies the presence of mesothelioma. Neoplasia or some other disease process should always be considered when pleural effusion is observed but ascites and jugular distention are absent. Many of the radiographic procedures (fluoroscopy, angiography, and pericardiography) used previously to identify the presence and cause of pericardial effusion have been supplanted by echocardiography.[66, 67]

ECHOCARDIOGRAPHY. Echocardiography is the safest, most practical, and most cost-effective diagnostic method for detecting pericardial effusion. It can detect very small (10 to 15 ml) accumulations of intrapericardial fluid.[68] Pericardial effusion is displayed on the echocardiogram as an anechoic space between the epicardium and pericardium (see Figs. 8–24 to 8–26; 29–15, 29–17). The amount of pericardial fluid can be estimated, but volume is not indicative of tamponade severity.[69] Rapid accumulation of small or moderate effusions can produce significant hemodynamic compromise, and large effusions accumulating over months may have little hemodynamic effect. Nonetheless, a large volume is more likely to be clinically significant.

Right and left ventricular dimensions are often diminished and the ventricular walls appear thicker than normal when pericardial effusion is severe and cardiac filling is impaired.[70] Diastolic collapse of the right atrium or right ventricle strongly suggests substantial elevation of intrapericardial pressure and cardiac tamponade (Figs. 29–15; 29–17).[71, 72] Unfortunately, neither the presence or absence of these findings is reliable for determining clinical significance or hemodynamic importance of an effusion.[73] Pericardial pressure can be markedly increased without diastolic collapse of the right atrium or ventricle if right ventricular filling pressures were elevated prior to development of pericardial effusion.[74] Conversely, significant collapse can occur with only minor elevations in intrapericardial pressure in patients that are volume depleted.[75] Thus, a diagnosis of cardiac tamponade should be based on the constellation of all clinical findings rather than on a single echocardiographic abnormality.

Echocardiography cannot provide a histologic diagnosis, but the location and appearance of many mass lesions are sufficiently consistent to permit reasonable speculation regarding their identity.[76–79] In dogs, a soft tissue mass arising from the right atrium is most likely a hemangiosarcoma, and a mass arising from the ascending aorta is likely to be a chemodectoma (Fig. 29–18).[75] Similarly, diffuse myocardial infiltration in

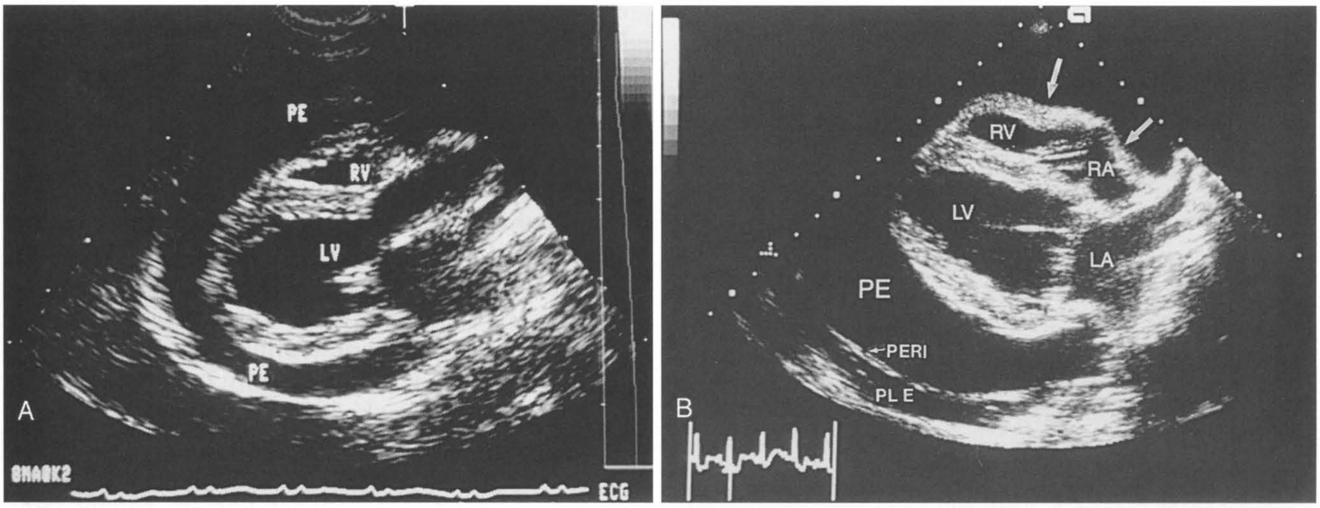


FIGURE 29-17

Two-dimensional echocardiograms recorded at the right parasternal location, long-axis view. Pericardial effusion *(PE)* appears as an anechoic (black) space between the epicardium and pericardium *(P)*. (A) Moderate pericardial effusion in a cat without cardiac tamponade. LV, left ventricle. (B) Severe pericardial effusion and cardiac tamponade in a dog. Notice diastolic collapse *(arrows)* of the right atrium *(RA)* and right ventricle *(RV)*. While not pathognomonic for cardiac tamponade, these findings suggest substantial elevation of intrapericardial pressure. This dog also has pleural effusion *(PL E)* appearing as a black anechoic space, which, combined with pericardial effusion, allows both sides of the pericardium to be visualized.

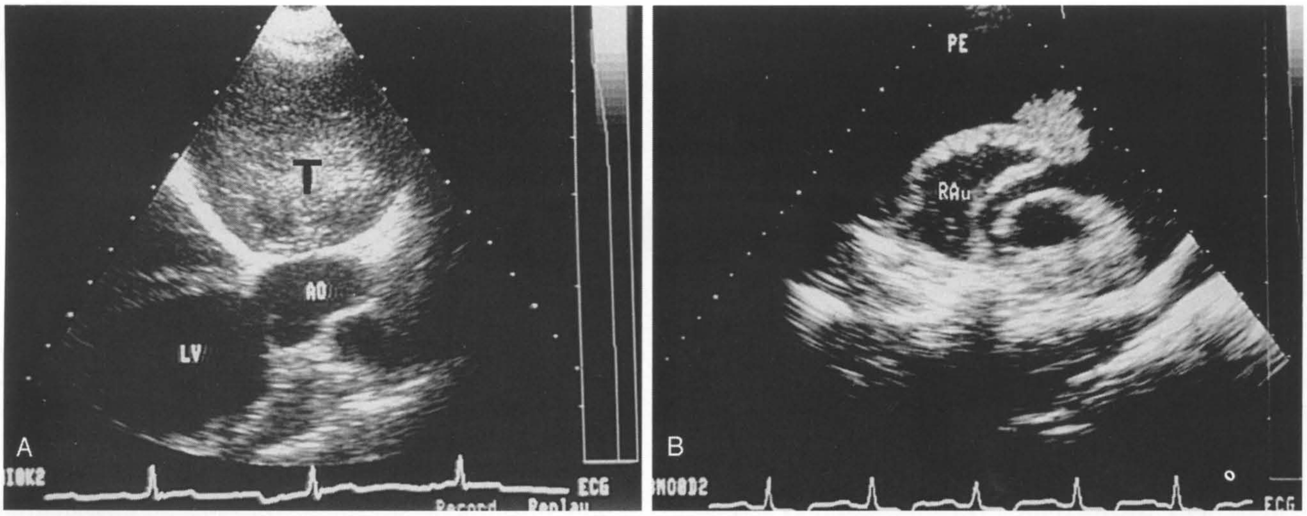


FIGURE 29-18

Two-dimensional echocardiograms recorded from the right parasternal location illustrating two common cardiac tumors of the dog. (A) Long-axis view of an aged dog showing a large (5.0 cm diameter) heart-base tumor *(T)* attached to the aortic root *(AO)*. Histologic examination revealed the mass to be chemodectoma. LV, left ventricle. (B) Basal short-axis view of a golden retriever dog's heart, depicting an irregular mass at the tip of the right auricle *(RAu)*. Histologic examination verified right auricular hemangiosarcoma. PE, pericardial effusion.

cats is highly suggestive of lymphosarcoma (Fig. 29–19).[78] Echocardiography also greatly simplifies the diagnosis of left atrial rupture secondary to degenerative valvular disease[40] and other defects such as pericardial cysts.[30] Transthoracic, two-dimensional echocardiography is 80 to 90 percent sensitive for detecting cardiac masses in dogs.[75] Transesophageal imaging is more sensitive but requires general anesthesia.[80] Owners should always be advised that false-negative studies are likely in dogs or cats with pericardial mesothelioma.

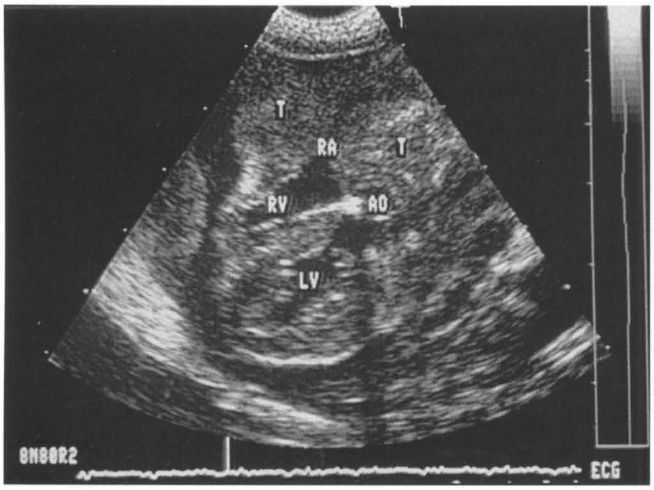


FIGURE 29-19

Two-dimensional echocardiogram recorded from the right parasternal position showing a long-axis view of a feline heart infiltrated by lymphosarcoma (same cat as in Fig. 29–11*B*). There is diffuse tumor *(T)* infiltration of the left and right atria and the entire heart base. RA, right atrium; RV, right ventricle; AO, aortic root; LV, left ventricle. Pericardial effusion is present.

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING. Gated studies are required to obtain detailed images of the heart unobscured by motion artifacts. Such studies are currently performed infrequently in companion animals, but they may be used more in the future to image the heart, pericardium, and mediastinum (Chapter 10). The value of CT and MRI for diagnosing constrictive pericarditis, pericardial cysts, and cardiac neoplasia in humans is well established.[81, 82]

PERICARDIOCENTESIS AND PNEUMOPERICARDIOGRAPHY. Pericardiocentesis is indicated whenever cardiac tamponade or infectious pericarditis is suspected.[42, 43, 67] We prefer a right-sided approach. The dog is positioned in left lateral recumbency to facilitate manual restraint of unsedated animals and to lessen the chance of coronary artery laceration. Thoracic radiography or echocardiography can indicate the best site to perform pericardiocentesis. Most often, the right fifth intercostal space at the costochondral junction is clipped and surgically prepared. The procedure can be performed in many dogs without sedation, but most cats require chemical restraint (Chapter 38). While monitoring the ECG, the operator advances an over-the-needle catheter, 2 to 5 inches long (depending on patient size), toward the heart. When fluid is obtained, the catheter is guided into the pericardial sac and the stylet is withdrawn. Palpable cardiac pulsations or VPCs on the ECG mandate slight withdrawal of the catheter and stylet. Once correct catheter location is ascertained, the pericardial sac is drained. When pericardiocentesis is successfully performed, the character of the arterial pulse improves and systemic blood pressure normal-

izes. The intrapericardial catheter can also be used to deliver drugs or other medicaments into the pericardial sac, or to inject air to perform pneumopericardiography (Fig. 29–16*C,D*).

Most pericardial effusions are bloody or blood tinged, and the clinician must ensure that the catheter is in the pericardial sac before withdrawing large volumes of fluid. If fluid source is uncertain, the sample should be centrifuged. The packed cell volume of pericardial fluid is usually much less than peripheral blood and its supernatant is typically xanthochromic. Also, pericardial fluid does not clot unless very recent hemorrhage into the pericardial sac has occurred.

Pericardial fluid samples should be submitted for laboratory analysis and cytologic evaluation. Most infections and some tumors, such as lymphosarcoma, can be reliably identified. Bacterial and fungal cultures are requested when the cytology report or fluid analysis results suggest an infectious process. However, it is very difficult to distinguish the common neoplastic effusions of dogs (hemangiosarcoma, heart-base tumors) from idiopathic effusions on the basis of red cell or white cell counts, protein content, or cytology.[83] Reactive mesothelial cells within the pericardial sac are commonly interpreted as being neoplastic (Fig. 36–12). Negative cytologic findings should also be interpreted cautiously as some cardiac and pericardial neoplasms do not readily exfoliate.

TREATMENT AND PROGNOSIS

IDIOPATHIC EFFUSIONS. Conservative treatment is recommended since about half of these dogs are cured by the initial pericardiocentesis.[39, 43] In the remainder, pericardial effusion recurs several days or weeks following initial pericardiocentesis. At this time, pericardiocentesis can simply be repeated or more aggressive strategies implemented. Corticosteroids are commonly administered to humans with recurrent idiopathic pericardial effusion.[84] Although such therapy has not been critically evaluated in animals, trial therapy with anti-inflammatory or immunosuppressive doses of corticosteroids should be considered. Most dogs with persistently recurring pericardial effusion are cured by surgical pericardiectomy. Some dogs with a recurring pleural effusion after pericardiectomy actually have a mesothelioma. The advantages of surgery are (1) previously unsuspected masses can be directly visualized, excised, or biopsied, (2) samples of pericardial tissue and regional lymph nodes can be obtained for histologic examination, and (3) subtotal pericardiectomy can be performed to prevent recurrence of cardiac tamponade or the development of constrictive pericarditis.[85] The disadvantages of this approach are those inherent in any exploratory surgery. Thoracoscopic pericardiectomy is a recently described alternative to surgical thoracotomy.[86, 87] This technique permits the examiner to visualize the heart and pericardium, to obtain biopsies, and to remove a substantial portion of the pericardium without the morbidity and expense of major surgery.

NEOPLASTIC EFFUSIONS. Prognosis for cardiac or pericardial neoplasia is generally poor. Associated effusions tend to be relentlessly progressive. Hemangiosarcoma, the most common tumor causing cardiac tamponade in dogs, is usually highly malignant. Currently used chemotherapy protocols are of limited utility.[88, 89] Some hemangiosarcomas, particularly those located on the right auricle, can be surgically excised, but most of these tumors already have or soon will spread to the lungs or other vital location. Pericardiocentesis provides limited benefit as pericardial effusion commonly redevelops within several days.[43] Pericardiectomy is rarely useful, and the prognosis is usually grave.

Heart-base tumors in some animals are slow growing and late to metastasize, whereas others are highly malignant. If the tumor is localized and accessible, surgical removal is advocated,[90] although it is not usually possible to achieve disease-free margins. Local recurrence can be anticipated in many cases. Extensive tumors, particularly those located on the posterior aspect of the aorta, are difficult or impossible to excise. In such cases, long-term relief from recurrent pericardial effusion may be realized following surgical, percutaneous balloon,[91] or thoracoscopic pericardiectomy.[86, 87] Lymphosarcoma of the heart and/or pericardium can be successfully treated by combination chemotherapy with or without radiation.[78] Pericardiocentesis may be required to relieve tamponade.

Metastatic tumors and pericardial mesotheliomas are often difficult to diagnose and are always difficult to treat. Diagnosis is usually accomplished by surgical pericardial biopsy. Histologic diagnosis of mesotheliomas can be difficult, necessitating ultrastructural analysis and immunohistochemical staining.[52] Biopsy of the lymph nodes draining the pericardial sac is also diagnostically helpful. In dogs and cats with pericardial mesothelioma, a recalcitrant pleural effusion often develops within several weeks of pericardiectomy; most die within a few months regardless of therapy, and chemotherapeutic efficacy has not been established.[92] Radiocolloids, such as phosphorus[32] colloidal chromic phosphate, are advocated as palliative treatment for malignant pericardial effusion resistant to chemotherapy.[93] Prospective trials are needed to evaluate therapy for malignant pericardial effusions in dogs and cats.

INFECTIOUS EFFUSIONS. Appropriate therapy requires adequate pericardial drainage combined with prolonged antimicrobial therapy.[94, 95] Surgical exploration of the thorax and pericardium is usually advisable; the pericardium can be excised, any foreign bodies removed, and adjacent organs inspected.[36] A notable exception

is pericarditis from feline infectious peritonitis in which pericardiocentesis, corticosteroids, and/or immunosuppressive drug therapy is advocated. Unfortunately, the usual outcome is death.

CONSTRICTIVE PERICARDITIS

In this difficult to diagnose disorder, cardiac filling is compromised by a nondistensible, thickened and fibrotic pericardium. Thirty cases have been reported in dogs, primarily males 2.5 to 9.5 years old.[96–98] No cases have yet been described in cats.

PATHOLOGY AND PATHOGENESIS. Constrictive pericarditis can develop from any form of chronic pericarditis, but dogs with chronic idiopathic effusions, mycotic pericarditis, neoplasia, or intrapericardial metallic foreign bodies are particularly vulnerable.[39, 43, 96–98] Some affected dogs have a thickened and fibrotic visceral and parietal pericardium, with extensive adhesions and only a small amount of pericardial fluid (Fig. 29–20). In most dogs, the parietal pericardium is more severely affected, with relative sparing of the visceral pericardium, and the volume of pericardial fluid is modestly increased. In extreme cases, the parietal pericardium may be up to 8 mm thick. Histologic findings include mesothelial proliferation, increased amounts of dense fibrous connective tissue, and inflammatory cell infiltrates of variable severity. Osseous pericardial metaplasia has been described in one young dog.[97]

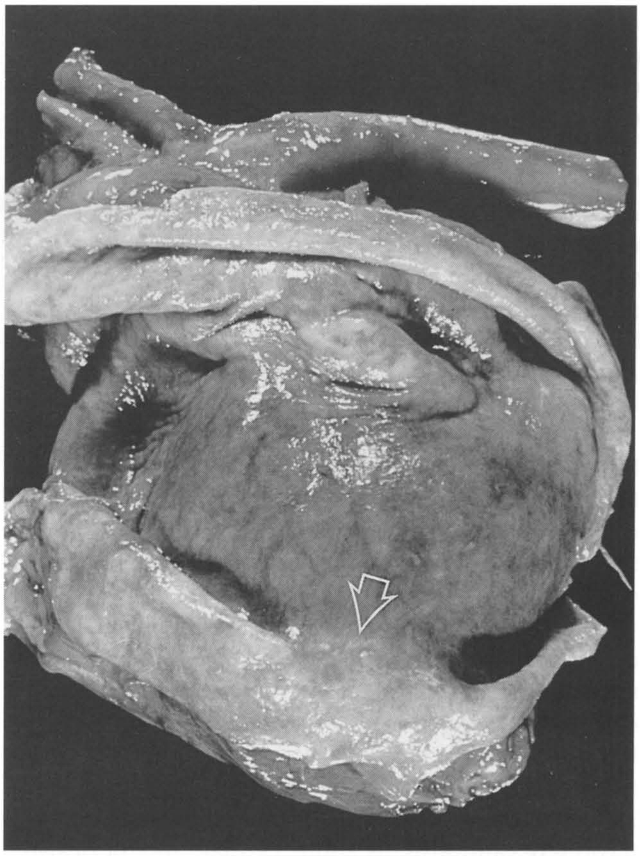


FIGURE 29-20

Canine heart viewed from the left lateral aspect. The thickened parietal pericardium has been incised and reflected upward toward the cardiac base and downward toward the right ventricle. Fibrosis and adhesions *(arrow)* between pericardium and epicardium have formed as a result of chronic infection with *Coccidioides immitis.* Hemodynamic studies indicated constrictive pericarditis.

PATHOPHYSIOLOGY. In most cases, early ventricular relaxation is normal, and ventricular filling proceeds rapidly until the limit of ventricular distensibility is reached. In mid-diastole, the thickened, noncompliant pericardium exerts its influence, abruptly limiting further expansion of the ventricle. Consequently, ventricular filling slows or ceases. The atrial and ventricular pressure tracings show a rapid y descent followed by an abrupt rise to an elevated diastolic plateau, distinguishing this disorder from effusive pericarditis.[99] This diastolic abnormality of the ventricular pressure tracing is frequently referred to as the "square root sign." Auscultation of a *pericardial knock* in early diastole is attributed to the vibrations produced by the blood when it strikes the nondistensible ventricular wall and decelerates. The prominent y descent may be absent when a small amount of pericardial fluid is present and the visceral pericardium is minimally involved.[100] This condition is referred to as *effusive-constrictive pericarditis.*[96, 97, 100]

Hemodynamic studies of dogs with constrictive pericarditis demonstrate elevation and equilibration of the pulmonary wedge; pulmonary artery; and RV, RA, LV, and LA diastolic pressures (Fig. 29–21). Such findings are anticipated when all cardiac chambers are encased in the same rigid pericardial sac. Several circumstances may foster exceptions to these observations. Localized areas of fibrosis may preferentially constrain only one cardiac chamber. In addition, diastolic pressures may also be disparate when filling pressures are normal or only slightly elevated. Such circumstances are encountered most commonly when diuretics have been administered. Rapid administration of intravenous solute usually suffices to reveal the patient's true circumstances (Fig. 29–22).

As constriction worsens and cardiac filling is more severely compromised, cardiac output declines. The usual decline in caval pressure associated with inspiration is often absent in dogs with constrictive pericarditis because the intrathoracic pressure changes associated with respiration are not transmitted to the cardiac chambers. This important observation requires careful examination of the jugular veins or the direct measurement of systemic venous pressure. In severe cases, systemic venous pressure may increase during inspiration, a clinical phenomenon known as *Kussmaul's sign.* Fluid

Hemodynamics of Constrictive Pericardiitis

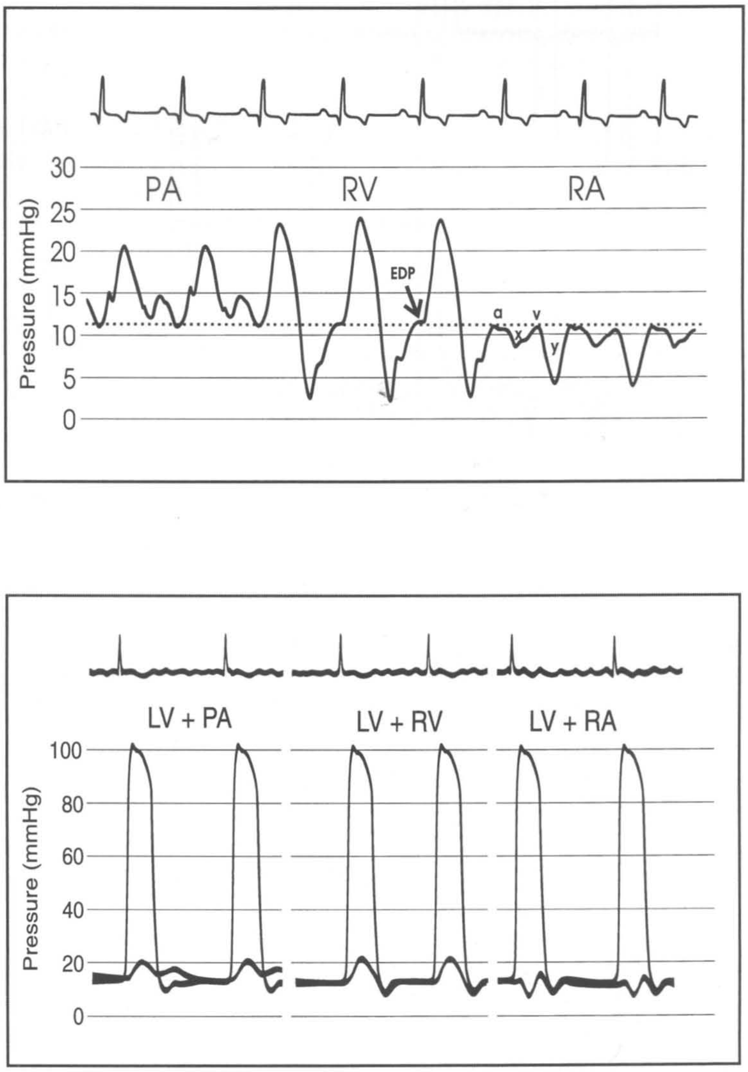


FIGURE 29-21

Hemodynamic abnormalities associated with constrictive pericarditis. In the top tracing, note the elevation and equilibration of diastolic pressures in the pulmonary artery *(PA)*, right ventricle *(RV)*, and right atrium *(RA)*. The rapid y descent followed by an abrupt rise to an elevated diastolic plateau in right atrial and right ventricular pressure tracings serves to distinguish constrictive pericarditis from pericardial effusion (compare with Fig. 29–13). In the bottom tracing, note the elevation and superimposition of diastolic pressures in the pulmonary artery *(PA)*, right ventricle *(RV)*, and right atrium *(RA)*.

retention is initiated by compensatory responses evoked by reduced cardiac output. As in patients with effusive pericarditis, there is an inadequate circulating atrial matriuretic peptide concentration.[101]

HISTORY AND PHYSICAL EXAMINATION. Right-sided heart failure (e.g., distended jugular veins; abdominal distention) is the most commonly noted abnormality. Less frequently, dyspnea, tachypnea, weakness, exercise intolerance, syncope, and weight loss are reported. Duration of illness varies from a few weeks to several months. In some cases, the medical history indicates a prior episode of idiopathic pericardial effusion or thoracic trauma. The heart sounds are often diminished in intensity, which is accentuated by pleural effusion. Cardiac auscultation is otherwise not helpful. The early diastolic *pericardial knock* described in humans with constrictive pericarditis is usually not audible. In dogs, however, systolic murmurs, gallop heart sounds, and systolic clicks occur, possibly due to concurrent chronic acquired valvular disease.

ELECTROCARDIOGRAPHY AND RADIOGRAPHY. The most common ECG changes are sinus tachycardia, prolonged P-wave duration, and reduced QRS complex amplitude.[96] Increased susceptibility to supraventricular tachycardia and atrial fibrillation has been reported.[96, 97] The cardiac silhouette may be normal or slightly enlarged and globoid. Pleural effusion is common, as is caudal vena caval enlargement. Fluoroscopy shows diminished motion of the cardiac borders, whereas angiocardiography sometimes indicates atrial enlargement and pericardial thickening as the endocardial-pericardial distance is increased over the right atrial surface. Compression of the RV outflow tract has been reported in two dogs with coccidioidal pericarditis.[96]

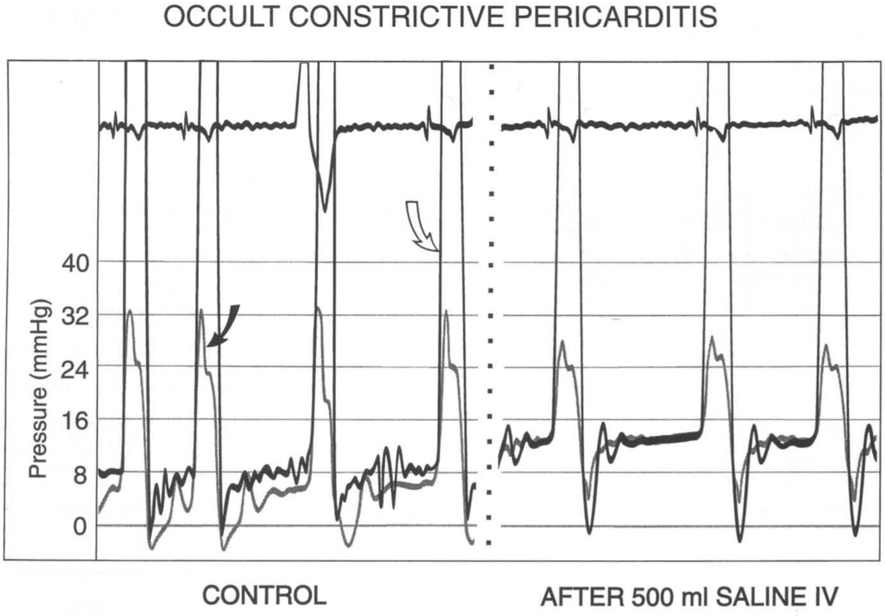


FIGURE 29-22

Recording of left ventricular *(open arrow)* and right ventricular *(solid arrow)* pressures in a dog with occult constrictive pericarditis before (control) and after intravenous saline infusion. Elevation and equilibration of pulmonary wedge, pulmonary artery, right ventricular, right atrial, left ventricular, and left atrial diastolic pressures may not be apparent in affected animals treated with high doses of diuretics. However, when filling pressures are raised by rapid administration of intravenous solute, the patient's true circumstances are made apparent. Notice changes in RV pressure trace and equilibration of RV and LV diastolic pressures after saline infusion.

ECHOCARDIOGRAPHY. Except in extreme cases, pericardial thickness cannot be determined accurately by echocardiography. Pericardial disease may not be suspected unless there is an increase in pericardial fluid. Most of the reliable echocardiographic changes reflect altered hemodynamics, including flat diastolic left ventricular wall motion, rapid E-F slope, early pulmonic valve opening, abnormal systolic or diastolic septal motion, and respiratory variation in the isovolumic relaxation time.[102, 103] Doppler echo interrogation of transmitral and pulmonary venous flows can be helpful in establishing a diagnosis.[104] In humans with constrictive pericarditis there is a marked decrease in pulmonary venous and transmitral flow velocities during expiration that is not observed in normal patients or in patients with restrictive myocardial disease. These echo changes have not yet been identified in dogs or cats.

THERAPY AND PROGNOSIS. Surgery is required to treat constrictive pericarditis successfully.[95, 105–107] Fibrosis is primarily limited to the parietal pericardium in most dogs, allowing subtotal parietal pericardiectomy. When the visceral pericardium and epicardium are significantly involved, surgery is more difficult and the outcome less favorable. In this circumstance, successful surgery requires decortication and removal of both the parietal and visceral pericardial layers. Reported complications include damage to coronary arteries, arrhythmias, and pulmonary thromboembolism. Nonetheless, most patients can be expected to survive surgery and experience substantial clinical improvement.

OTHER CARDIAC NEOPLASMS

ETIOLOGY. In dogs, the overall prevalence of cardiac neoplasia, including hemangiosarcoma and heart-base tumors, was reported to be 0.17 percent of hospital admissions (based on the Veterinary Medical Database at Purdue with 638,867 cases from 1982 to 1993).[108] Primary cardiac tumors in dogs include chondro(sarco)ma, fibro(sarco)ma, hemangio(sarco)ma, leiomyo(sarco)ma, lipofibroma, lymphangioendothelioma, mesothelioma, myxofibroma, myxoma, neurofibroma, rhabdomyo(sarco)ma, and ectopic thyroid, mixed spindle cell, and round cell sarcomas.[109] Metastatic carcinomas and various types of sarcomas have also been reported, including chemodectoma and parathyroid and thyroid carcinomas.

Tumors infiltrating the heart can be exceptionally difficult to diagnose, and most are fortuitously discovered when echocardiography is performed for some other reason. When metastatic or infiltrative lesions are observed, a careful search for the primary tumor site should be conducted. A cardiac biopsy may be required to establish an antemortem diagnosis.

An obstructing mass in the right atrium of a dog is most likely to be a hemangiosarcoma, but myxomas are also prone to develop in this location. Right ventricular outflow tract tumors are usually chemodectomas or ectopic thyroid tumors. Masses compressing the left atrium and obstructing pulmonary venous inflow are usually chemodectomas arising from the caudal aspect of the aorta, but ectopic thyroid and parathyroid tumors also may develop in this location. The left ventricular inflow region may be occluded by myxoma or other tumor arising from the left atrium or mitral valve. Metastatic tumors and rhabdomyosarcomas tend to infiltrate the myocardium, induce arrhythmias, or cause pericardial effusion.

In cats, the overall prevalence of cardiac neoplasia was less than 0.03 percent of hospital admissions (based on the Veterinary Medical Database at Purdue

with 210,388 cases from 1982 to 1993).[108] Other than lymphoma, feline cardiac tumors include chemodectoma, metastatic hemangiosarcoma, fibrosarcoma, pulmonary carcinoma, and mammary gland carcinoma.

THERAPY. Treatment of cardiac neoplasia often involves a combination of surgery, chemotherapy, and radiation.[44–46, 87–93] A cardiac surgeon and oncologist should be consulted prior to initiating therapy.

References

1. Buchanan JW. Causes and prevalence of cardiovascular disease. *In* Kirk RW, Bonagura JD (eds). Kirk's Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1992, p 647
2. Holt D, Van Winkle T, Schelling C, et al. Correlation between thoracic radiographs and postmortem findings in dogs with hemangiosarcoma. J Am Vet Med Assoc 200:1535, 1992
3. Holt JP. The normal pericardium. Am J Cardiol 26:455, 1970
4. Santamore WP, Constantinescu MS, Bogen D, et al. Nonuniform distribution of normal pericardial fluid. Basic Res Cardiol 85:541, 1990
5. Goto Y, Le Winter MM. Nonuniform regional deformation of the pericardium during the cardiac cycle in dogs. Circ Res 67:1114, 1990
6. Bouvy BM, Bjorling DE. Pericardial effusion in dogs and cats. Part 1. Normal pericardium and causes and pathophysiology of pericardial effusion. Compendium Small Anim Med Pract Vet 13:417, 1991
7. Miller AJ, Jain S, Levin B. Radiographic visualization of lymphatic drainage of heart muscle and pericardial sac in the dog. Chest 59:271, 1971
8. Eliskova M, Eliska O, Miller AJ. The lymphatics of the canine parietal pericardium. Lymphology 27:181, 1994
9. Shabetai R. The Pericardium. New York, Grune & Stratton, 1981
10. Hamilton DR, Dani RS, Semlacher RA, et al. Right atrial and right ventricular transmural pressures in dogs and humans. Effects of the pericardium. Circulation 90:2492, 1994
11. Hoit BD, Dalton N, Bhargava V, Shabetai R. Pericardial influences on right and left ventricular filling dynamics. Circ Res 68:197, 1991
12. Reed JR, Thomas WP. Hemodynamics of progressive pneumopericardium in the dog. Am J Vet Res 45:302, 1984
13. Applegate RJ, Johnston WE, Vinten-Johansen J, et al. Restraining effect of intact pericardium during acute volume loading. Am J Physiol 262:H1725, 1992
14. Coons MS, Woloszyn TT, Folliguet TA, et al. Pericardiotomy improves left ventricular compliance during sepsis-induced pulmonary artery hypertension. Am Surg 58:32, 1992
15. Hunter S, Smith GH, Angelini GD. Adverse hemodynamic effects of pericardial closure soon after open heart surgery. Thorac Surg 53:425, 1992
16. Freeman GL, LeWinter MM. Pericardial adaptations during chronic cardiac dilation in dogs. Circ Res 54:294, 1984
17. Janicki JS. Influence of the pericardium and ventricular interdependence on left ventricular diastolic and systolic function in patients with heart failure. Circulation 81:15, 1990
18. van der Gaag I, van der Luer RJT. Eight cases of pericardial defects in the dog. Vet Pathol 14:14, 1977
19. Reed JR. Pericardial Diseases. *In* Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 495
20. Köhler H. Ruptur des Herzbeutels beim Hund. Dtsch Tierärztl Wochenschr 65:489, 1958
21. Teuscher E. Ein merkwürdiger Fall von Myokardnekrose beim Hund. Dtsch Tierärztl Wochenschr 65:409, 1958
22. Neiger R. Peritoneopericardial diaphragmatic hernia in cats. Compendium Small Anim Med Pract Vet 18:461, 1996
23. Evans SM, Biery DN. Congenital peritoneopericardial diaphragmatic hernia in the dog and cat: A literature review and additional case histories. Vet Radiol 21:108, 1980
24. Eyster GE, Evans AT, Blanchard GL, et al. Congenital pericardial diaphragmatic hernia and multiple cardiac defects in a litter of collies. J Am Vet Med Assoc 170:516, 1977
25. Lunney J. Congenital peritoneal pericardial diaphragmatic hernia and portacaval shunt in a cat. J Am Anim Hosp Assoc 28:163, 1992
26. Bellah JR, Whitton DL, Ellison GW, Phillips L. Surgical correction of concomitant cranioventral abdominal wall, caudal sternal, diaphragmatic, and pericardial defects in young dogs. J Am Vet Med Assoc 195:1722, 1989
27. Bellah JR, Spencer CP, Brown DJ, Whitton DL. Congenital cranioventral abdominal wall, caudal sternal, diaphragmatic, pericardial, and intracardiac defects in cocker spaniel littermates. J Am Vet Med Assoc 194:1741, 1989
28. Saperstein G, Leipold HW. Congenital defects in domestic cats. Feline Pract 18:43, 1976
29. Hay WH, Woodfield JA, Moon MA. Clinical echocardiographic, and radiographic findings of peritoneopericardial diaphragmatic hernia in two dogs and a cat. J Am Vet Med Assoc 195:1245, 1989
30. Sisson D, Thomas WP, Reed J, et al. Intrapericardial cysts in the dog. J Vet Intern Med 7:364, 1993
31. Marion J, Schwartz A, Ettinger SJ. Pericardial effusion in a young dog. J Am Vet Med Assoc 157:1055, 1979
32. Loehr WM. Pericardial cysts. AJR Am J Roentgenol 68:584, 1952
33. Gibbs C, Gaskell CJ, Darke PGG, et al. Idiopathic pericardial haemorrhage in dogs: A review of fourteen cases. J Small Anim Pract 23:483, 1982
34. Berg RJ, Wingfield WE, Hoopes PJ. Idiopathic hemorrhagic pericardial effusion in eight dogs. J Am Vet Med Assoc 185:988, 1984
35. de Madron E, Prymak C, Hendricks J. Idiopathic hemorrhagic pericardial effusion with organized thrombi in a dog. J Am Vet Med Assoc 191:324, 1987
36. Aronson LR, Gregory CR. Infectious pericardial effusion in five dogs. Vet Surg 24:402, 1995
37. Thomas WP, Sisson D, Bauer TG, et al. Detection of cardiac masses in dogs by two-dimensional echocardiography. Vet Radiol 25:65, 1984
38. Fuentes VL, Long KJ, Darke PGG, et al. Purulent pericarditis in a puppy. J Small Anim Pract 32:585, 1991
39. Thomas WP. Pericardial disorders. *In* Ettinger SJ (ed). Textbook of Veterinary Internal Medicine. 3rd ed. Philadelphia, WB Saunders, 1989, p 1132
40. Sisson D. Acquired valvular heart disease in dogs and

cats. *In* Bonagura J (ed). Cardiology. New York, Churchill Livingstone, 1987, p 59
41. Straw BE, Ogburn P, Wilson JW. Traumatic pericarditis in a dog. J Am Vet Med Assoc 174:501, 1979
42. Berg RJ, Wingfield W. Pericardial effusion in the dog: a review of 42 cases. J Am Anim Hosp Assoc 20:721, 1983
43. Thomas WP, Reed JR. Pericardial disease. *In* Kirk RW (ed). Current Veterinary Therapy. Vol IX. Philadelphia, WB Saunders, 1986, p 364
44. Aronsohn M. Cardiac hemangiosarcoma in the dog: a review of 38 cases. J Am Vet Med Assoc 187:922, 1985
45. Ogilvie GK, Powers BE, Mallinckrodt CH, et al. Surgery and donorubicin in dogs with hemangiosarcoma. J Vet Intern Med 10:379, 1996
46. Kleine LJ, Zook BC, Munson TO. Primary cardiac hemangiosarcomas in dogs. J Am Vet Med Assoc 157:326, 1970
47. Hayes HM. An hypothesis for the aetiology of canine chemoreceptor system neoplasms, based upon an epidemiological study of 73 cases among hospital patients. J Small Anim Pract 16:337, 1975
48. Patnaik AK, Liu SK, Hurvitz AI, et al. Canine chemodectoma (extra-adrenal paragangliomas)—a comparative study. J Small Anim Pract 16:785, 1975
49. Hayes HM, Sass B. Chemoreceptor neoplasia: a study of the epidemiological features of 357 canine cases. Zentralbl Veterinarmed (A) 35:401, 1988
50. Cheville NF. Ultrastructure of canine carotid body and aortic body tumors. Comparison with tissues of thyroid and parathyroid origin. Vet Pathol 9:166, 1972
51. Walsh KM, Diters RW. Carcinoma of ectopic thyroid in a dog. J Am Anim Hosp Assoc 20:665, 1984
52. McDonough SP, MacLachlan NJ, Tobias AH. Canine pericardial mesothelioma. Vet Pathol 29:256, 1992
53. Thrall DE, Goldschmidt MH. Mesothelioma in the dog: six case reports. J Am Vet Radiol Soc 19:107, 1978
54. Tilley LP, Owens JM, Wilkins RJ. Pericardial mesothelioma with effusion in a cat. J Am Anim Hosp Assoc 11:60, 1975
55. Harpster NK. The cardiovascular system. *In* Holzworth J (ed). Diseases of the Cat— Medicine and Surgery. Vol I. Philadelphia, WB Saunders, 1987, p 911
56. Rush JE, Keene BW, Fox PR. Pericardial disease in the cat: a retrospective evaluation of 66 cases. J Am Anim Hosp Assoc 26:39, 1990
57. Fossum TW, Miller MW, Rogers KS, et al: Chylothorax associated with right-sided heart failure in five cats. J Am Vet Med Assoc 204:84, 1994
58. Reddy PS, Curtiss EI, O'Toole J, et al. Cardiac tamponade; hemodynamic observations in man. Circulation 58:265, 1978
59. Reddy PS, Curtiss EI, Uretsky BF. Spectrum of hemodynamic changes in cardiac tamponade. Am J Cardiol 66:1487, 1990
60. Louie EK, Hariman RJ, Wang Y, et al. Effect of acute pericardial tamponade on the relative contributions of systolic and diastolic pulmonary venous return: a transesophageal pulsed Doppler study. Am Heart J 129:124, 1995
61. Stokhof AA, Overduin LM, Mol JA, et al. Effect of pericardiocentesis on circulating concentrations of atrial natriuretic hormone and arginine vasopressin in dogs with spontaneous pericardial effusion. Eur J Endocrinol 130:357, 1994
62. Fitchett DH, Sniderman AD. Inspiratory reduction in left heart filling as a mechanism of pulus paradoxus in cardiac tamponade. Can J Cardiol 6:348, 1990
63. Brown J, MacKinnon D, King A, et al. Elevated arterial pressure in cardiac tamponade. N Engl J Med 327:463, 1992
64. Bonagura JD. Electrical alternans associated with pericardial effusion in the dog. J Am Vet Med Assoc 178:574, 1981
65. Sacks E, Widman LE. Nonlinear heart model predicts range of heart rates for 2:1 swinging in pericardial effusion. Heart Circ Physiol 33:H1716, 1993
66. Thomas WP, Reed JR, Gomez JA. Diagnostic pneumopericardiography in dogs with spontaneous pericardial effusion. Vet Radiol 25:2, 1984
67. Miller MW, Sisson DD. Pericardial diseases. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 1032
68. Berry CR, Lombard CW, Hager DA, et al. Echocardiographic evaluation of cardiac tamponade in dogs before and after pericardiocentesis: four cases (1984–1986). J Am Vet Med Assoc 192:1597, 1988
69. D'Cruz IA, Hoffman PK. A new cross-sectional echocardiographic method for estimating the volume of large pericardial effusions. Br Heart J 66:448, 1991
70. Di Segni E, Feinberg MS, Sheinowitz M, et al. Left ventricular pseudohypertrophy in cardiac tamponade: an echocardiographic study in a canine model. J Am Coll Cardiol 21:1286, 1993
71. Kronzon I, Cohen ML, Winer HE. Diastolic atrial compression: a sensitive sign of cardiac tamponade. J Am Coll Cardiol 2:770, 1983
72. Armstrong WF, Schilt BF, Helper DJ, et al. Diastolic collapse of the right ventricle with cardiac tamponade: an echocardiographic study. Circulation 65:1491, 1982
73. Reydel B, Spodick DH. Frequency and significance of chamber collapses during cardiac tamponade. Am Heart J 119:1160, 1990
74. Vaska K, Wann LS, Sagar K, et al. Pleural effusion as a cause of right ventricular diastolic collapse. Circulation 86:609, 1992
75. Labib SB, Udelson JE, et al. Echocardiography in low pressure cardiac tamponade. Am J Cardiol 63:1156, 1989
76. Thomas WP, Sisson D, Bauer TG, Reed JR. Detection of cardiac masses in dogs by two-dimensional echocardiography. Vet Radiol 25:65, 1984
77. Fruchter AM, Miller CW, O'Grady MR. Echocardiographic results and clinical considerations in dogs with right atrial/auricular masses. Can Vet J 33:171, 1992
78. Brummer DG, Moise NS. Infiltrative cardiomyopathy responsive to chemotherapy in a cat with lymphoma. J Am Vet Med Assoc 195:1116, 1989
79. Weyman AE. Principles and Practice of Echocardiography. 2nd ed. Philadelphia, Lea & Febiger, 1994, p 391
80. Reeder GS, Khandheria BK, Seward JB, et al. Transesophageal echocardiography and cardiac masses. Mayo Clin Proc 66:1101, 1991
81. Gouliamos A, Andreou J, Steriotis J, et al. Detection of pericardial heart disease by computed tomography. Clin Radiol 35:397, 1984
82. Soulen RL. Magnetic resonance imaging of great vessel, myocardial, and pericardial disease. Circulation 84 (3 suppl): I311, 1991
83. Sisson D, Thomas WP, Ruehl WW. Diagnostic value of pericardial fluid analysis in the dog. J Am Vet Med Assoc 51:184, 1984
84. Shabetai R. Acute pericarditis. Cardiol Clin 8:639, 1990
85. Hehrlein FW, Moosdorf R, Pitton M, et al. The role of pericardiectomy in pericardial disorders. Eur Heart J 12 (Suppl D):7, 1991

86. Hazelrigg SR, Mack MJ, Landreneau RJ, et al. Thoracoscopic pericardiectomy for effusive pericardial disease. Ann Thorac Surg 56:792, 1993
87. Richter KP, Jackson J, Hart JR. Thoracoscopic pericardiectomy in 12 dogs. Abstract. J Vet Intern Med 10:164, 1996
88. de Madron E, Helfand SC, Stebbins KE. Use of chemotherapy for treatment of cardiac hemangiosarcoma in a dog. J Am Vet Med Assoc 190:887, 1987
89. Brown NO, Patnaik AK, MacEwan EG. Canine hemangiosarcoma. J Am Vet Med Assoc 186:56, 1985
90. Wagner SD, Breznock EM. Surgical management of pericardial and intramyocardial disease, including chemodectomas. *In* Bojrab MJ (ed). Current Techniques in Small Animal Surgery. 2nd ed. Philadelphia, Lea & Febiger, 1983
91. Ziskind AA, Pearce AC, Lemmon CC, et al. Percutaneous balloon pericardiotomy for the treatment of cardiac tamponade and large pericardial effusions: description of technique and report of first 50 cases. J Am Coll Cardiol 21:1, 1993
92. Krarup-Hansen A, Hansen HH. Chemotherapy in malignant mesothelioma: a review. Cancer Chemother Pharmacol 28:319, 1991
93. Sprengelmeyer JT, McDermott RL. Phosphorus-32-colloidal chromic phosphate: treatment of choice for malignant pericardial effusion. J Nucl Med 31:2034, 1990
94. Majid AA, Omar A. Diagnosis and management of purulent pericarditis. J Thorac Cardiovasc Surg 102:413, 1991
95. Bennet EV. Purulent pericarditis. J Thorac Cardiovasc Surg 85:531, 1983
96. Thomas WP, Reed JR, Bauer TG, Breznock EM. Constrictive pericardial disease in the dog. J Am Vet Med Assoc 184:546, 1984
97. Wright KN, DeNovo RC, Patton CS, et al. Effusive-constrictive pericardial disease secondary to osseous metaplasia of the pericardium in a dog. J Am Vet Med Assoc 209:2091, 1996
98. Campbell SL, Forrester SD, Johnston SA, et al. Chylothorax associated with constrictive pericarditis in a dog. J Am Vet Med Assoc 206:1561, 1995
99. Fowler NO. Constrictive pericarditis: its history and current status. Clin Cardiol 18:341, 1995
100. Hancock EW. Fundamentals of clinical cardiology. On the elastic and rigid forms of constrictive pericarditis. Am Heart J 100:917, 1980
101. Anand IS, Ferrari R, Kalra GS, et al. Pathogenesis of edema in constrictive pericarditis. Studies of body water and sodium, renal function, hemodynamics, and plasma hormones before and after pericardiectomy. Circulation 83:1880, 1991
102. Hatle LK, Appleton CP, Popp RL. Differentiation of constrictive pericarditis and restrictive cardiomyopathy by Doppler echocardiography. Circulation 79:357, 1989
103. Chandraratna PA. Echocardiography and Doppler ultrasound in the evaluation of pericardial disease. Circulation 84 (3 Suppl):I303, 1991
104. Mancuso L, D'Agostino A, Pitrolo F, et al. Constrictive pericarditis versus restrictive cardiomyopathy: the role of Doppler echocardiography in differential diagnosis. Int J Cardiol 31:319, 1991
105. Tuna IC, Danielson GK. Surgical management of pericardial disease. Cardiol Clin 8:683, 1990
106. Brockington GM, Zebed J, Pandian NG. Constrictive pericarditis. Cardiol Clin 8:645, 1990
107. DeValeria PA, Baumgartner WA, Casale AS, et al. Current indications, risks, and outcome after pericardiectomy. Ann Thorac Surg 52:219, 1991
108. Ware WA. Cardiac neoplasia. *In* Bonagura J (ed). Kirk's Current Veterinary Therapy. Vol XII. Philadelphia, WB Saunders, 1995, p 873
109. Sisson D, Thomas WP. Myocardial diseases of the dog and cat. *In* Ettinger SJ, Feldman E (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1994, p 995

30

Canine Heartworm Disease

CLAY A. CALVERT
CLARENCE A. RAWLINGS
JOHN W. McCALL

EPIZOOTIOLOGY

Heartworm disease occurs throughout the United States.[1] Infection rates of up to 45 percent occur within 150 miles of the Atlantic coast from Texas to New Jersey and along the Mississippi River and its major tributaries. The infection rate is lower in the remainder of the United States and southern Canada. There are many other important world endemic areas, including Japan, Australia, and some Mediterranean countries.[2]

The risk of heartworm infection is correlated with signalment and lifestyle.[3] Dogs housed outside are four to five times more likely to be infected than indoor dogs; sporting breeds generally experience the highest infection rates. Male canine infections were reported four times more often than female infections,[3] although one study indicated that spayed females housed entirely outside were at greatest risk for heartworm infection.[3a] Dogs as young as 1 year of age can have heartworm infection, but most infected dogs are 3 to 6 years old when diagnosed.[4] The hair coat does not affect the probability of heartworm infection.[3]

LIFE CYCLE *(Dirofilaria immitis)*

Heartworm infection is spread by many different mosquito species, and the geographic distribution of infection is directly related to that of the susceptible mosquitoes.[5] The season and feeding habits of specific mosquito species may determine the timing of heartworm infection in susceptible dogs.[6] Cats are less likely to be bitten by mosquitoes, but at least one species *(Culex)* is more likely than other mosquitos to bite felines.[6]

Female mosquitoes serve as intermediate hosts after obtaining blood meals from dogs with circulating *D. immitis* microfilariae. Microfilariae develop within the mosquito and are capable of infecting another dog within 2 to 2.5 weeks.[7, 8] Development of microfilariae to infective third-stage larvae (L_3) is heat dependent. Incubation requires average daily temperatures greater than 57°F. When the average daily temperature for any 30-day period is under 65°, transmission of infective heartworm larvae is unlikely. Infective larvae enter the host's skin via the mosquito's bite wound. After 3 to 4 months, young adults (L_5) enter the vascular system and travel to the small pulmonary arteries. Microfilariae are first seen in the blood approximately 6 months after infective larvae enter their new host. Numbers usually increase markedly during the next 6 months, after which microfilarial concentration frequently declines.[2]

PATHOGENESIS OF HEARTWORM DISEASE

Disease severity and onset are determined, in part, by the number of adult heartworms, which varies from 1 to more than 250 worms per dog.[9] Dogs with a high heartworm burden generally experience greater pulmonary vascular disease and more severe pulmonary hypertension than do lightly infected dogs. In an average-sized (25-kg) dog, nearly all the heartworms reside in the caudal pulmonary arteries until the heartworm number exceeds 25. As their numbers increase, more are found in the right ventricle and pulmonary arteries. The right atrium frequently contains heartworms when more than 50 worms are present, and infections with such high numbers of worms frequently result in their extension into the vena cava.[10] Dogs infected with more than 100 worms are at substantial risk of developing the vena caval syndrome.[8–10]

Large numbers of worms can mechanically obstruct the flow of blood, whether they are located in the venae cavae, right atrium, or pulmonary arteries.[10a] In this circumstance, physical worm extraction may immediately improve cardiovascular function and clinical signs. However, in most infected dogs, clinical signs primarily reflect the host's responses to the worms and their excretory products, rather than their physical presence. Clinical consequences include pneumonitis, granuloma formation, pulmonary endarteritis, thromboembolism, pulmonary hypertension, and cor pulmonale.

HOST RESPONSE TO LIVE HEARTWORMS

Damage to the pulmonary arterial endothelial lining is evident within 3 days of experimental transplantation of adult heartworms into healthy dogs.[11] Prior to melarsomine administration, it is important that the patient's cardiopulmonary complications be improved as much as possible using oxygen, heparin, or other supportive measures as required. Patients with severe heartworm disease may have marked pulmonary hypertension, thromboembolism and associated dyspnea, hypoxemia, coughing, and hemoptysis. Anemia, thrombocytopenia, disseminated intravascular coagulopathy, and ascites are often present. Echocardiography may reveal severe RV dilation with decreased contractility and reduced LV and aortic root size due to inadequate RV output. Severely affected dogs whose cardiopulmonary status cannot be stabilized may die prior to or within a few weeks of melarsomine treatment. Heartworms in the pulmonary arteries produce endothelial swelling, widened intercellular junctions, sloughing of longitudinal strips of endothelium, and adhesion of activated leukocytes and platelets to the damaged area (Fig. 30–1). This increases vascular endothelial permeability to serum proteins and water, with leakage into the perivascular interstitium.[11, 12] Trophic factors, such as platelet-derived growth factor (PDGF), are released by activated platelets and leukocytes. They stimulate migration and multiplication of smooth muscle cells within the tunica media. Within 3 weeks, rapidly dividing smooth muscle cells migrate from the media to the intima and multiply.

Pulmonary arterial villi induced by heartworm-infected dogs consist of rapidly dividing smooth muscle cells and the collagen produced by them (Fig. 30–2). They range in size from a few microns to several millimeters (Fig. 30–3). Endothelial damage and villous proliferation are most pronounced in the caudal and accessory lung lobes, reflecting the distribution pattern of adult heartworms.[11–14] With relatively brief heartworm infections, vascular endothelial resolution occurs within 4 to 6 weeks following adulticide treatment.[8, 9]

Arteriographic abnormalities are apparent within a few weeks of adult heartworm residence. Caudal and

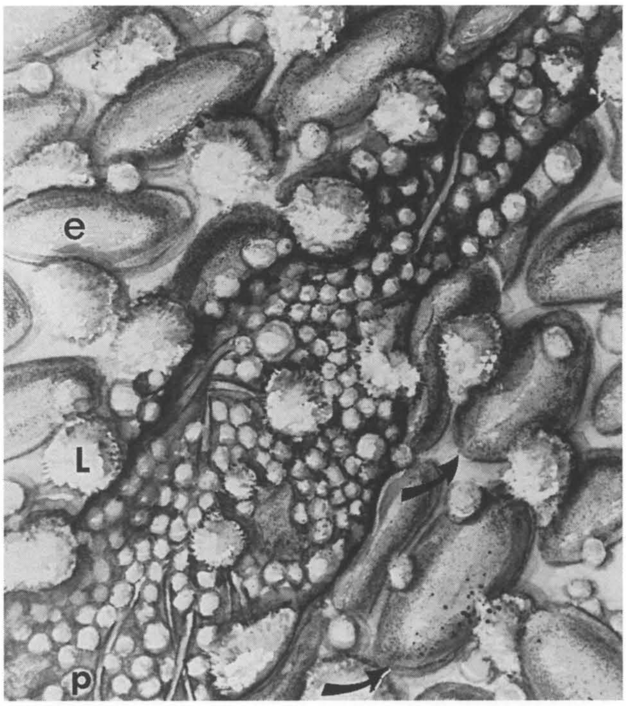


FIGURE 30–1

Drawing of the surface of the pulmonary artery as it appears by scanning electron microscopy. This injury can be seen within 3 days after heartworms arrive within the pulmonary circulation. Endothelial cells *(E)* are rounded and disoriented compared with normal endothelial surfaces. Leukocytes *(L)* that are ruffled adhere to a strip of arterial wall that has been denuded of endothelium. Adhesion and activation of platelets *(p)* and leukocytes result in release of trophic factor(s) that stimulates smooth muscle cells to form villi (see Figure 30–2). (From Rawlings CA, Keith JC Jr, Schaub RG: Development and resolution of pulmonary disease in heartworm infection: Illustrated review. J Am Anim Hosp Assoc 17:711, 1981, with permission.)

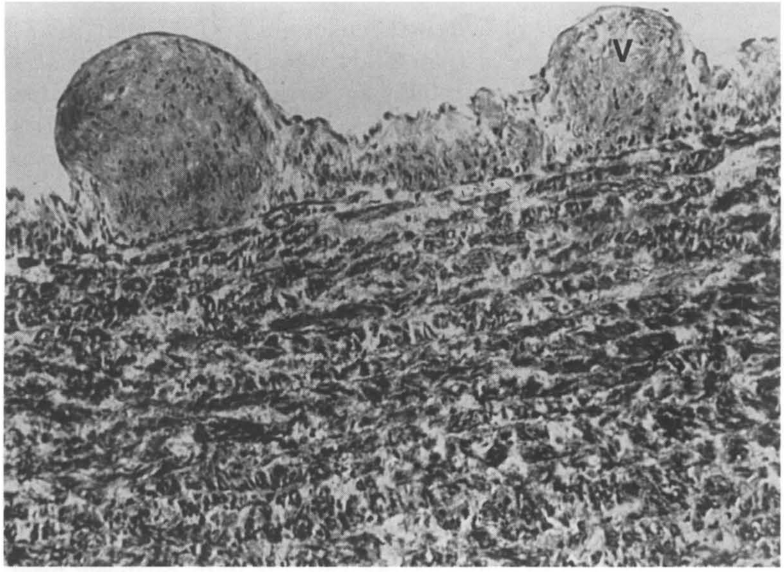


FIGURE 30–2

Light micrograph of villi *(V)* projecting from the surface of a heartworm-injured pulmonary artery into its lumen. Villi are composed of rapidly dividing smooth muscle cells and fibrous connective tissue. The base of the villi appears to arise from the tunica media. The luminal surface, when viewed by scanning electron microscopy, is covered by endothelium-like cells.

accessory lobar arteries dilate, become tortuous, develop aneurysms, and lose their normal tapering arborization (Fig. 30–4). Smaller arteries appear to be abruptly pruned. Blood flow is diverted from obstructed areas of the lung to the more normal lung lobes. Arterial dilation and tortuosity, as well as pulmonary hypertension, can resolve following reduction or elimination of heartworms by adulticide treatment.[15, 16] Central arterial lesions resolve more completely than peripheral ones.[15–17] Decreases in the diameter of the large, elastic pulmonary arteries are due, in large part, to the decline of pulmonary arterial pressure.[16, 18] Residual fibrosis of the more distal arteries often remains.

Increased interstitial densities occur on thoracic ra-

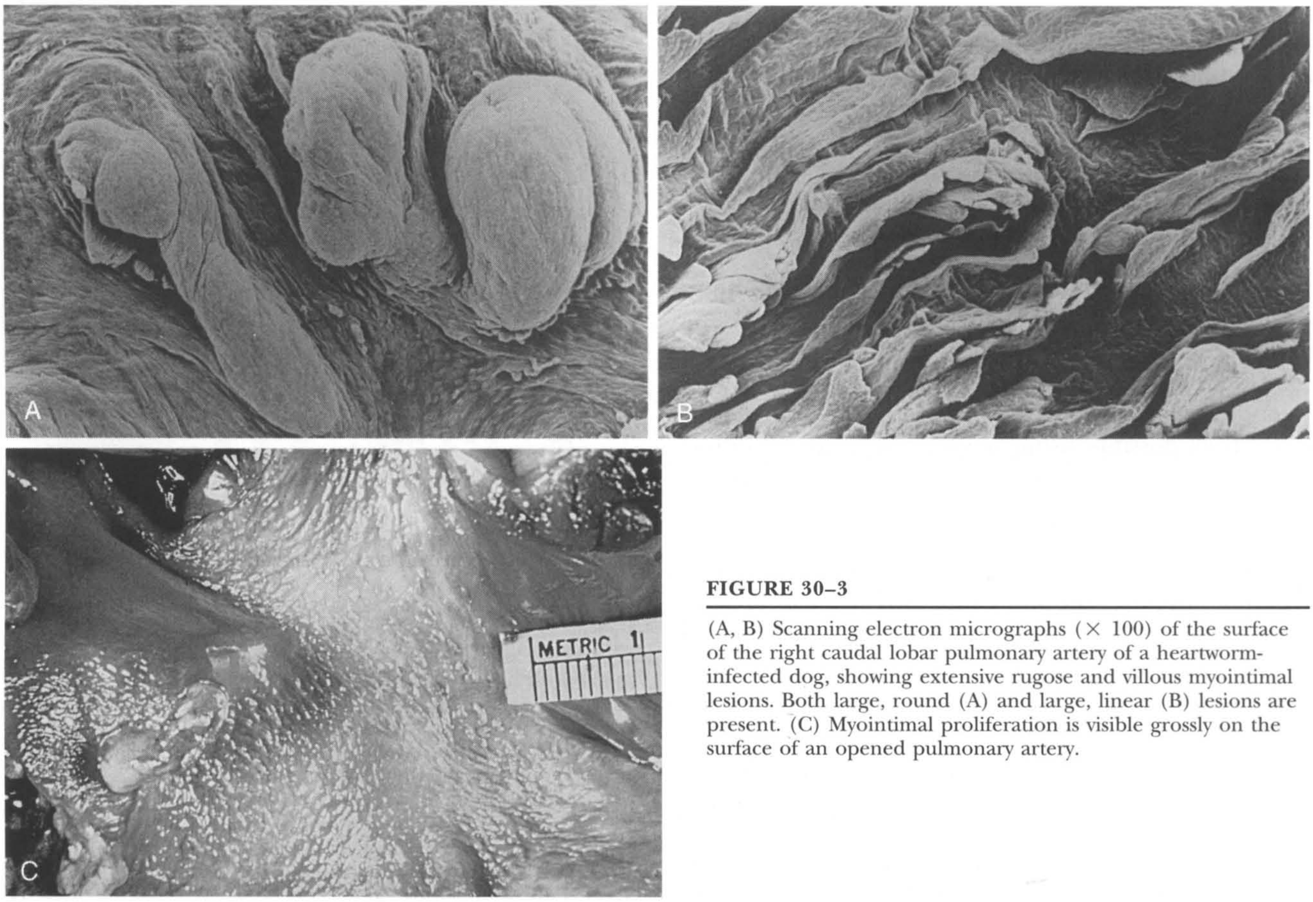


FIGURE 30–3

(A, B) Scanning electron micrographs (× 100) of the surface of the right caudal lobar pulmonary artery of a heartworm-infected dog, showing extensive rugose and villous myointimal lesions. Both large, round (A) and large, linear (B) lesions are present. (C) Myointimal proliferation is visible grossly on the surface of an opened pulmonary artery.

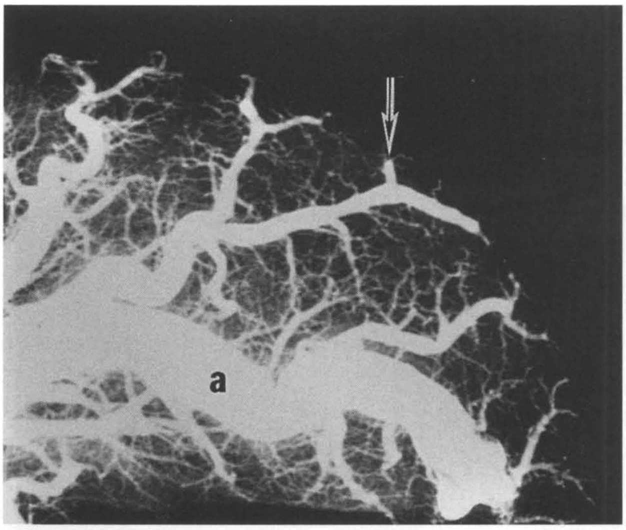


FIGURE 30–4

Postmortem pulmonary arteriogram from a dog with heartworm infection. The right caudal lobar artery *(a)* is dilated and severely tortuous. Branches from the lobar artery are also dilated and tortuous, whereas their branches appear abruptly pruned *(arrow)*. The dilated arteries are large enough to contain heartworms and sustain the most severe villous proliferation.

diographs and probably result from perivascular fluid leakage and inflammatory cell accumulation.[17] Increased vascular permeability can also produce an alveolar pattern (Fig. 30–5). Alveolar densities typically resolve rapidly with appropriate treatment, whereas interstitial changes often persist, even after elimination of adult heartworms.[2] Much of the vascular pathology can be prevented with platelet-inhibiting drugs.[18, 19]

HOST RESPONSE TO DEAD HEARTWORMS

The most severe pulmonary lesions occur after adult heartworms have died and their fragments have been swept distally into small pulmonary arteries. The response at the pulmonary arterial surface is an exacerbation of that described for live heartworms. Exuberant villous proliferation is complicated by the development of thrombi and granulomatous inflammation about the dead heartworms.[11, 15, 16, 18] Blood flow to certain lung regions becomes severely impaired[16, 17] (Fig. 30–6). Caudal lung lobes may become severely consolidated, with impaired capacity for gas exchange or blood flow (Fig. 30–7).[16–18] Severe coughing, dyspnea, and hemoptysis may develop, and increased vascular resistance can produce acute right heart failure.[2]

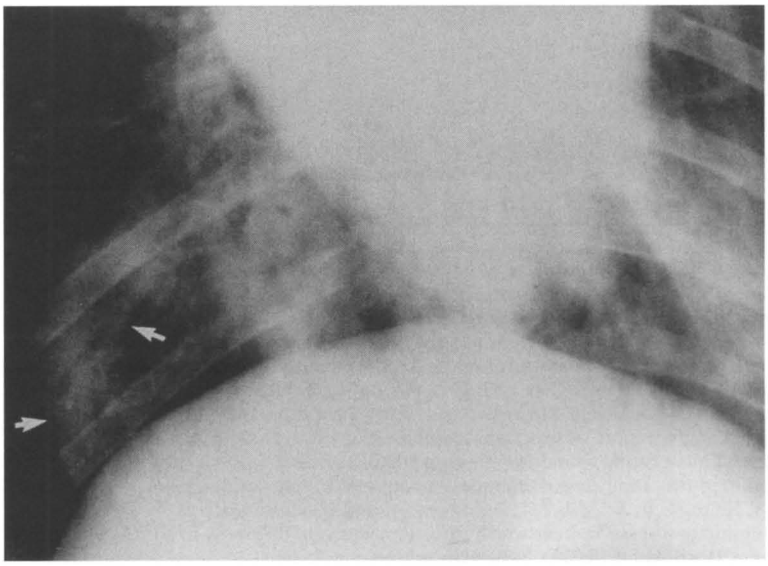
OCCULT HEARTWORM INFECTIONS

The percentage of occult heartworm infection varies between 5 and 67 percent.[20–26] It probably represents 10 to 20 percent of the total infection in most regions of the United States.

Occult infections occur in several circumstances.[27–29] Microfilariae are not produced during the prepatent period in dogs with single sex heartworm infections, or when adult worms are rendered infertile as a result of drug therapy.[27, 28] In addition, occult infections can result when microfilariae are destroyed by immune-mediated processes. Prior to the introduction of the macrolide antibiotics for heartworm prevention, unisex and prepatent infections accounted for 57 to 85 percent of occult infections in the United States, Australia, and Japan.[20–26] The extensive use of ivermectin and milbemycin oxime during the past few years has probably greatly increased the percentage of drug-induced occult heartworm cases.[30, 31] Unisex infections occur more frequently in regions of low heartworm incidence, as fewer larvae are inoculated into the host. Prepatent infections are common during the winter

FIGURE 30–5

Ventrodorsal thoracic radiograph depicting mixed interstitial alveolar lung disease in the caudal lobes. The right caudal lobar artery is large and tortuous *(arrows)*.



and spring months in dogs that have been infected during the previous late summer or fall. Microfilariae are absent from the circulation for 6 months following inoculation. Mature female worms contribute most of the antigen detected by serologic tests, and circulating antigen is not detectable until 7 or 8 months postinoculation.

Immune-mediated occult infections result from host hypersensitivity to microfilarial antigens.[32–35] Antibody (IgG) excess predisposes to occult infections. Antibody-dependent leukocyte adhesion to microfilariae in the pulmonary capillaries results in microfilarial entrapment.[33, 35] Microfilaria-leukocyte complexes are engulfed by phagocytic cells of the pulmonary reticuloendothelial system, and granulomatous inflammation ensues. Immune-mediated destruction of microfilariae can produce specific clinical syndromes, such as allergic pneumonitis and pulmonary eosinophilic granulomatosis. Up to 70 percent of dogs with severe pulmonary arterial disease have occult heartworm infections, suggesting a large contribution of the immune response to arterial lesions.

Occult heartworm infections also result from long-term administration (≥6 months) of macrolide agents at prophylactic doses.[30, 36] Even when macrolides are withdrawn, microfilariae do not reappear for months, if at all.[30, 36] Initiation of monthly macrolide prophylaxis in dogs harboring immature worms consistently induces occult infections if the worms are not killed.[31] Microfilarial production is also suppressed by high ivermectin doses (≥200 μg/kg) used to treat other parasites.[37] Drug-induced occult heartworm infections can usually be detected by antigen-detecting serologic tests.

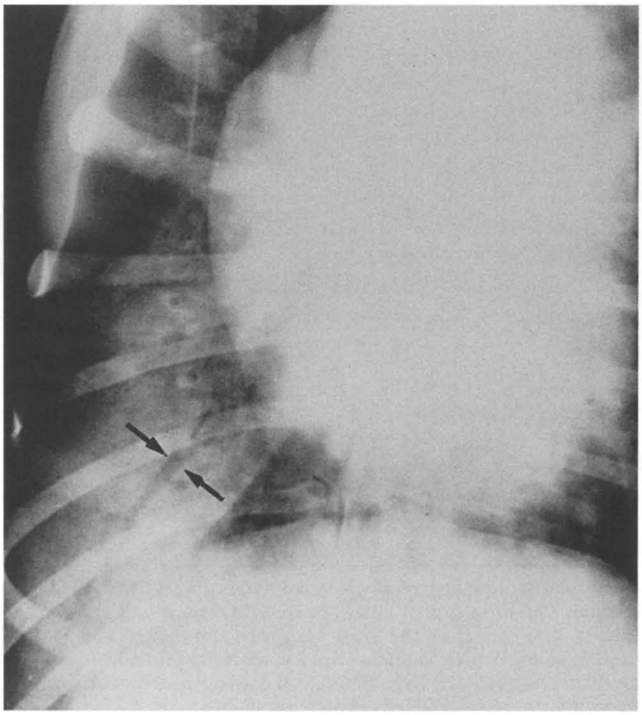


FIGURE 30–7

Ventrodorsal radiograph demonstrating partial consolidation of the right caudal lung lobe of a dog 17 days postadulticide treatment. Air bronchograms are present *(arrows)*, indicating an alveolar lung pattern. The animal exhibited coughing, hemoptysis, tachypnea, pyrexia, tachycardia, pale mucous membranes, lethargy, and anorexia.

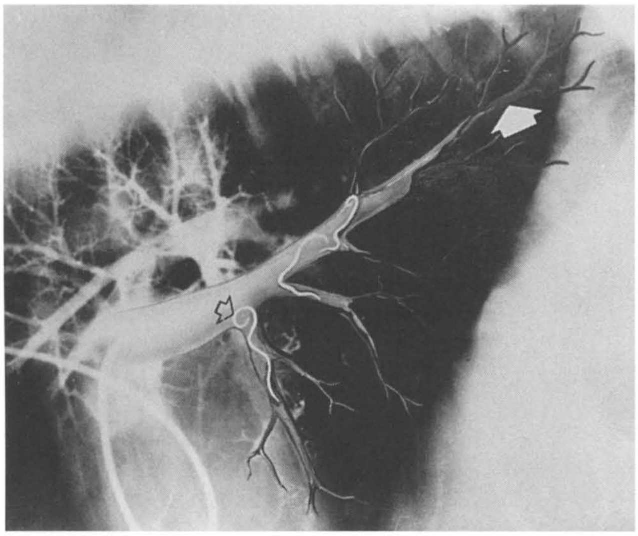


FIGURE 30–6

Right pulmonary arteriogram (enhanced by an illustrator) demonstrating obstruction of blood flow to the right caudal lung lobe following adulticide treatment. Distal arteries *(large white arrow)* do not fill, probably due to intraluminal thrombosis, exuberant villous proliferations, or dead heartworm fragments with surrounding granulomatous inflammation. Dead and dying heartworms *(open arrow)* are characterized radiographically by a crumpled silhouette in the area of sluggish blood flow. Despite severe angiographic obstruction of arterial flow, this dog did not have clinical cardiopulmonary signs, probably because it was strictly confined following thiacetarsamide treatment. (From Rawlings CA, Keith JC Jr, Schaub RG: Development and resolution of pulmonary disease in heartworm infection: Illustrated review. J Am Anim Hosp Assoc 17:711, 1981, with permission.)

CLINICAL EVALUATION OF HEARTWORM-INFECTED DOGS

CLINICAL SIGNS OF HEARTWORM INFECTION

Clinical signs reflect the number of heartworms present, the duration of infection, and host response. Most dogs are asymptomatic. Coughing and dyspnea are the most common signs and are usually associated with parenchymal disease of the caudal lung lobes. Edema and inflammation around the arterioles and small airways may stimulate coughing.

Eventually, increased vascular resistance and pulmonary hypertension develop in heartworm-infected

dogs. This decreases exercise ability and results in right ventricular dilation, hypertrophy, and failure. Increased pulmonary vascular resistance impedes arterial blood flow and increases right ventricular work. Severe disease restricts the ability to recruit arteries for the high blood-flow rate needed for exercise.[16] Dyspnea results from the pulmonary vascular and parenchymal changes induced by adult heartworms, accompanying increase in pulmonary vascular resistance, and the resulting ventilation-perfusion mismatch. Arterial hypoxemia exacerbates pulmonary hypertension.[38]

Signs of right-sided congestive heart failure, such as ascites, develop late. Physical examination may then reveal splitting of the second heart sound, a right apical gallop, distended jugular veins, and abnormal lung sounds. Signs of heart failure are often exacerbated by exercise. Cardiac cachexia develops with advanced heartworm disease and chronic right heart failure. Hemoptysis occasionally occurs in untreated dogs but is more commonly observed following adulticide therapy. It results from vascular and airway wall rupture, probably induced by coughing. Bleeding usually occurs in the caudal lung lobes, where vascular and parenchymal changes are most severe.

CLASSIFICATION OF HEARTWORM-INFECTED DOGS

Based on historical findings, clinical signs, physical examination, thoracic radiograph assessment, and laboratory data, heartworm-infected dogs can often be placed into one of three classes (Table 30–1).[39] *Class 1* dogs are asymptomatic or mildly symptomatic; *class 2* dogs have moderate disease; and *class 3* dogs have severe heartworm disease. Important historical and physical findings suggesting more advanced heartworm disease include exercise intolerance, persistent or severe coughing, syncope, hemoptysis, weight loss, and ascites. Thoracic radiography most accurately reflects the severity of heartworm disease.

The prognosis for dogs with class 1 disease is excellent. Successful therapy should return the dog to preinfection status. Dogs with class 3 disease often do poorly. For large numbers of worms accompanied by severe clinical signs, worm extraction and antiplatelet or anticoagulant treatment combined with cage confinement or an alternative melarsomine dihydrochloride treatment regimen should be considered.[39–42,a] Such modifications may produce over 80 percent survival, compared with 40 to 50 percent survival when standard therapy is used.[39, 40]

DIAGNOSIS OF HEARTWORM INFECTION

The classic screening method that relied on identifying microfilariae in venous blood has largely given way to highly sensitive and specific immunodiagnostic serologic tests. Antigen-detecting serologic tests have gained advantage because they can detect occult infections, which comprise about 20 percent of the total number of heartworm cases. For this reason, the incidence of falsely negative heartworm antigen tests is far less than that of any microfilariae-detecting method.[43]

IMMUNODIAGNOSTIC TESTING

Commercially available immunodiagnostic tests detect heartworm infection more accurately than microfilarial concentration tests. Heartworm antigen tests are very specific (98%), and false-positive results are uncommon when the tests are properly performed.[44–48] Nonetheless, false-positive results pose a problem when screening dogs where heartworm prevalence is low.

The predictive value of a positive test (the percent of test-positive dogs that actually have heartworm infection) depends on test specificity and disease prevalence.[43–45] In areas of low heartworm prevalence, the positive predictive accuracy of an antigen test is much

TABLE 30–1
Classification of Heartworm Disease Severity Based on Signs, Physical Examination, and Radiographic Findings

Class	Clinical Signs	Examination Findings	Radiographic Findings
1	None to occasional cough	Normal examination	No lesions
2	Occasional cough and mild-to-moderate exercise intolerance	Increased lung sounds Fair general condition	Slight pulmonary arterial enlargement. Circumscribed perivascular density plus mixed alveolar-interstitial lesions
3	Persistent cough, moderate-to-severe exercise intolerance Weight loss, cachexia Respiratory distress Overt right heart failure General loss of condition	Increased lung sounds Accentuated or split S_2 Right apical gallop Tachypnea, dyspnea	Moderate-to-severe pulmonary arterial enlargement RV enlargement Diffuse and severe pulmonary infiltrates

lower than in areas of high infection prevalence. Weakly positive test results should always be repeated, preferably utilzing a different test. A positive microfilarial concentration test resolves the dilemma of uncertain antigen test results.

Serologic tests detect the presence of mature female worms; live male worms contribute little or nothing to a positive antigen test.[48, 49] Thus, falsely negative serology test results are most likely to occur when the infection is recent (less than 7 months postinoculation), or when female worms are absent or number only a few. Antigenemia is absent or too low to be detected up to 5 months postinoculation of L_3, and false-negative test results can occur for up to 8 months.[48] This is important when evaluating dogs with prepatent infections that were infected late in the previous summer and tested in March and April.

Although some commercial antigen test kits can detect the presence of a single adult female worm,[49] sensitivities are somewhat variable.[48] Falsely negative test results are common with less than three female worms, particularly if they are younger than 1 year old. A protein expressed by L_4 heartworm larvae has recently been identified and cloned by recombinant techniques.[49a] This antigen has been used experimentally to detect prepatent, single sex, and male worm infections, suggesting that improvements in serologic testing will overcome existing deficiencies.[49a]

Currently, three companies (IDEXX Laboratories, Inc., Synbiotics Animal Health, and Rhone Merieux, Inc.) produce all the heartworm serology tests available in the United States. Most of the available tests are enzyme-linked immunosorbent assays (ELISA) but one test (VetRed, Rhone Merieux, Inc.) is a hemagglutination-based kit, and one (ICT GOLD HW) is an immunochromatographic assay.[50–51a] Some tests require serum or plasma, whereas others can be performed using whole blood. Most tests employ positive and negative controls; some are more convenient when large numbers of tests are to be run simultaneously; and some require more time to perform. Sensitivities and specificities of some of the rapidly performed tests are less than desirable. The various serology tests also differ from each other relative to ease of interpretation.

Antigen-detecting serologic tests are semiquantitative—that is, a rapidly developing, strong reaction usually indicates a relatively large worm burden.[52] This information may be useful, as dogs with higher worm burdens are at risk for more severe pulmonary thromboembolic events following treatment. Dogs with a high concentration of heartworm antigen should be meticulously evaluated and treated with caution.

Most heartworm-infected dogs in the continental United States have low worm burdens as assessed serologically, and thoracic radiographs and clinical signs are adequate to estimate disease severity and the risk of postadulticide complications. High worm burdens and high levels of circulating antigen are much more common in the Caribbean and Hawaii.

MICROFILARIAE TESTING

Testing for microfilariae is indicated in all heartworm-infected dogs. Microfilarial screening is essential in all dogs receiving or intended to receive diethylcarbamazine. Microfilarial concentration tests (e.g., modified Knott's or filter tests) are reasonably accurate, and the choice is a matter of tradition and individual bias. Routinely, a drop of whole blood is held back from the concentration test sample for a direct smear. If the direct smear is positive and the microfilariae are identified as *D. immitis*, the more time-consuming concentration test is unnecessary. Since the direct smear is less sensitive than concentration tests, a negative result does not rule out infection. Over 90 percent of all dogs with circulating microfilariae have adult infections.[53] The most accurate heartworm screening tests in dogs 6 to 7 months of age are the microfilariae-detecting tests, because detectable antigen concentrations are not usually present until 8 months postinoculation.

The microfilariae of *D. immitis* must be distinguished from those of *Dipetalonema reconditum*. The direct wet smear prepared from a drop of venous blood can be used for differentiation. In general, the concentration of *D. immitis* microfilariae is higher than that seen with *D. reconditum*, in which usually only a few are seen. The microfilariae of *D. immitis* tend to gyrate without progressive movement across the field, whereas those of *D. reconditum* exhibit progressive, undulating movement across the field. The *D. immitis* microfilariae are larger, with a diameter as large as or larger than that of canine red blood cells.[2] More specific morphologic criteria have been defined based on the appearance of microfilariae fixed in 2 percent formalin for the Knott's test. Microfilariae of *D. immitis* are usually over 290 microns in length and 6 microns in width, whereas *D. reconditum* are less than 275 microns long and 6 microns wide. *D. immitis* has a tapered anterior end; *D. reconditum* has a blunt anterior end and a cephalic hook.[2]

Only rarely are microfilariae detected when antigen test results are negative. For this reason, the combined use of these tests for routine screening purposes is not recommended.

CLINICAL EVALUATION OF HEARTWORM-INFECTED DOGS

Determination of hematocrit, blood urea nitrogen (BUN); and urine specific gravity is adequate for

young and asymptomatic dogs, but we prefer to obtain a complete blood count with platelet count, serum chemistry profile, and urinalysis in all candidates for adulticide therapy. Testing for microfilariae is indicated in all dogs in which diagnosis was initially made by serology. Conversely, an adult antigen test is useful whenever the diagnosis is made by identification of microfilariae.

Although the vast majority of microfilariae-positive dogs have live adult worms, the worm burden cannot be predicted by the number of circulating microfilariae. In contrast, a strong antigen test reaction usually indicates a high worm burden. Such dogs are at increased risk of severe postadulticide thromboembolic complications. Comparison of preadulticide with 3-month postadulticide antigen testing can identify persisting adult worms and their relative numbers.

Thoracic radiographs provide more information about the severity of heartworm disease than any other single test (see later).[54, 55] Only in selected cases does an electrocardiogram (ECG) or echocardiogram provide useful information.

CLINICAL PATHOLOGY

Most of the hematologic abnormalities associated with heartworm infections are mild. Increased numbers of eosinophils and basophils are a common but nonspecific finding in heartworm-infected dogs. Such changes are often observed in dogs with occult heartworm infections or allergic pneumonitis. The absence of eosinophilia or basophilia is not predictive of freedom from heartworms. Eosinophil and basophil numbers are frequently higher in dogs with *Dipetalonema reconditum* infections than in dogs with *D. immitis*.[56]

A mild, nonregenerative anemia is commonly observed in dogs with chronic and severe heartworm infection. A more severe, regenerative anemia is sometimes seen in dogs with the caval syndrome or severe pulmonary arterial disease. Regenerative anemia results from intravascular hemolysis and is often accompanied by hemoglobinuria. It occurs most commonly in dogs with caval syndrome or severe pulmonary thromboembolic disease. Thrombocytopenia is observed in dogs with low-grade or chronic disseminated intravascular coagulation, and in dogs with severe pulmonary arterial disease with thromboembolism. Inflammatory leukograms may occur in dogs with large pulmonary thrombi or infiltration by plasma and inflammatory cells.

Hypoalbuminemia occurs in dogs with chronic or severe heartworm disease either as the result of protein-losing glomerulonephropathy (amyloidosis or immune complex disease), or as a manifestation of right-sided congestive heart failure. Hepatic insufficiency occasionally contributes to hypoalbuminemia in dogs with chronic right-sided congestive heart failure. More often, hypoproteinemia is dilutional in such patients as excess sodium and water is retained and plasma volume increases. Proteinuria is also a common sequela of heartworm disease. Although proteinuria is mild in most patients, moderate-to-severe proteinuria indicates severe glomerular disease, particularly when associated with hypoalbuminemia. Irreversible glomerular disease is uncommon but results in renal failure and the nephrotic syndrome.

RADIOGRAPHIC FINDINGS

Thoracic radiography is the most useful and cost-effective diagnostic procedure available for characterizing the severity of heartworm disease. Common pulmonary arterial abnormalities include (1) increased prominence of the main pulmonary artery, (2) enlarged lobar pulmonary arteries, (3) enlargement or abnormal tapering of the peripheral pulmonary arteries, (4) interstitial and alveolar lung changes, and (5) right ventricular enlargement.[57–59] Arterial lesions and associated parenchymal disease tend to be more severe in the caudal lung lobes.[16] The diameter of the caudal lobar arteries at their intersection with the 9th rib should be no larger than the narrowest diameter of the 9th rib as viewed on the dorsal-ventral projection.[2, 57, 58] The lateral radiograph is used to measure the right cranial lobar artery and to characterize the parenchymal pattern in the caudal lung lobes. The diameter of the right cranial lobar artery at the intersection with the right 4th rib should not exceed the narrowest diameter of the 4th rib.

Excessive emphasis is often placed on identifying right ventricular enlargement. Radiographic assessment is subjective, as the morphology of the cardiac silhouette varies with breed.[57–59] Overinterpretation of right ventricular enlargement in round-chested dogs is common and may cause a false-positive diagnosis of heartworm disease.[59]

The frequency of associated radiographic abnormalities varies. In one referral institution, 86 percent of 200 microfilaria-positive dogs had radiographic changes typical of heartworm infection.[57] Approximately 10 to 15 percent had evidence of severe right ventricular enlargement.[57, 58] These percentages vary with the spectrum of disease seen in a particular practice area. Dogs that are more heavily infected with heartworms usually have more severe radiographic signs (Fig. 30–8). Approximately 60 to 70 percent of heartworm-infected dogs have enlargement of the main pulmonary artery.[57, 58] Lobar arterial disease (enlargement and/or tortuosity) is present in approximately one half of our patients and is easily assessed.[57, 58] When the diameters of the lobar arteries

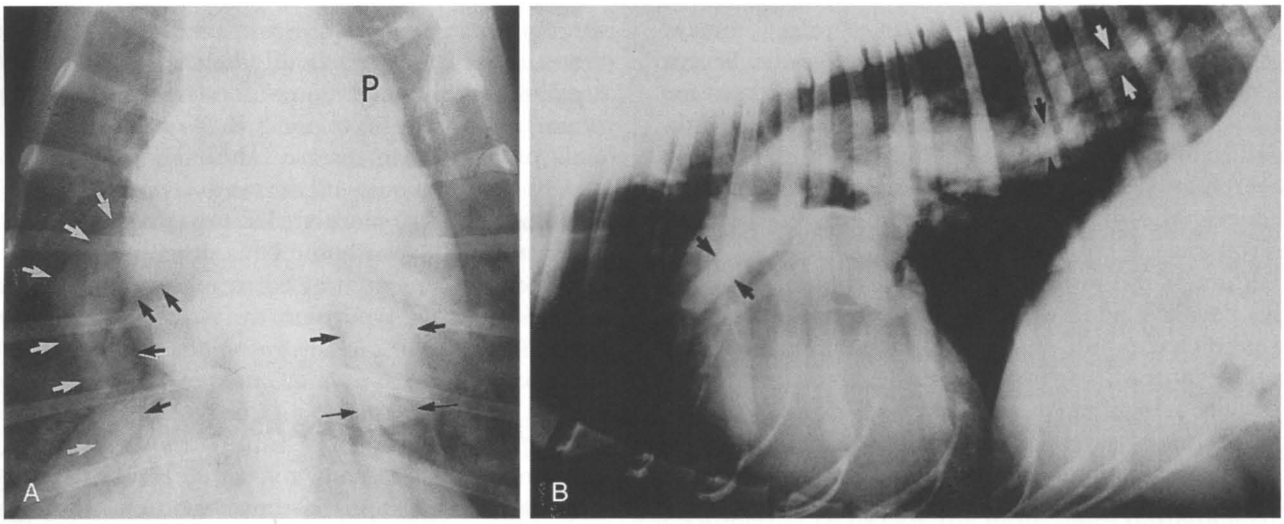


FIGURE 30–8

Dorsoventral (A) and lateral (B) thoracic radiographs of two dogs with severe heartworm disease. The lobar arteries are very large and tortuous *(arrows)*. There is marked enlargement of the main pulmonary artery *(P)* and right side of the heart.

are increased, the likelihood of heartworm infection is high.[57, 58]

The most severe parenchymal lung changes occur following adulticidal treatment when dead heartworms are washed into the distal pulmonary arteries. Radiographic signs include alveolar and interstitial changes (see Fig. 30–7). Similar changes are observed less frequently prior to adulticide treatment. Typical alveolar patterns include radiographic densities with ill-defined fluffy margins that coalesce, that contain air bronchograms, that exhibit lobar distribution, or are centrally located. These are most commonly observed adjacent to the lobar pulmonary arteries in the caudal and intermediate lung lobes.[59–61]

Alveolar lung patterns usually regress rapidly following successful adulticide treatment. These infiltrates and associated clinical signs often resolve quickly with corticosteroid treatment.[59, 60] Increased interstitial densities indicate fibrosis produced by chronic disease and are generally irreversible.

ELECTROCARDIOGRAPHY

Electrocardiography is not a very useful test for heartworm disease. At least 90 percent of infected dogs have normal ECGs.[54] Severe pulmonary arterial disease is always present by the time the ECG criteria for right ventricular hypertrophy become unequivocal. In over 50 percent of such dogs, overt right-sided congestive heart failure (CHF) is present.[40, 41, 55] Thus, the main value of the ECG is to characterize the nature of an auscultated arrhythmia.

ECHOCARDIOGRAPHY

Echocardiography can be used to (1) evaluate right-sided heart function, (2) estimate the number and location of heartworms (Fig. 30–9; see also Fig. 31–5), and (3) determine the severity of pulmonary hypertension (Doppler studies). When pulmonic or tricuspid valve insufficiency is present, pulmonary artery pressures can be quickly and rapidly estimated by measuring the peak velocities of the regurgitant jets. Dogs with severe pulmonary hypertension typically have a dilated right ventricle with reduced contractility, right atrial enlargement, and enlarged pulmonary arteries. Not all dogs with severe heartworm disease have high worm burdens. Class 2 dogs have a higher mean antigen concentration than class 3 dogs. This indicates a reduced worm burden but more severe vascular disease in the latter group.[61a] The prognosis and form of treatment selected are affected by worm burden as well as the severity of pulmonary vascular disease.

HEARTWORM ADULTICIDE THERAPY

Nearly all heartworm-infected dogs are acceptable candidates for treatment. Success rates for class 1 and class 2 dogs are very high. Class 3 dogs often can be helped, although the risk of severe, life-threatening, post-adulticidal pulmonary complications is higher. Modifications of treatment protocols used in dogs with milder disease are strongly advised for class 3 patients and class 2 dogs with high worm burdens. Dogs with

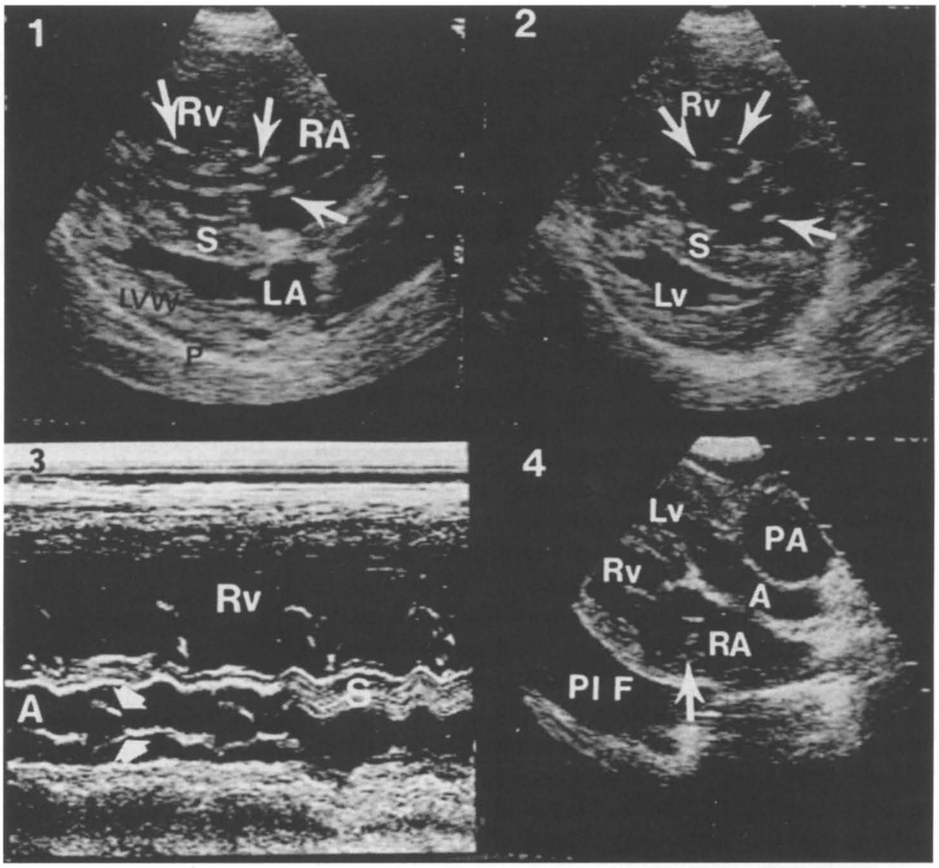


FIGURE 30–9

Echocardiograms of a beagle-cross dog with severe heartworm disease. *Frame 1:* Two-dimensional echo (right parasternal long axis view) showing heartworms in the right atrium *(RA)* and right ventricle *(Rv)*, which appear as white, echogenic specks *(arrows)*. The RA and Rv are dilated whereas the left atrium *(LA)* and left ventricle are reduced in size. The interventricular septum *(S)* is flattened in this view and in the short axis view in *Frame 2. Frame 3:* M-mode echocardiogram recorded at the level of the right ventricle *(Rv)* and aorta *(A)*. The aortic valve leaflets are seen to close gradually during systole *(arrows)* due to decreased forward stroke volume from heartworm disease. Normally, they stay open throughout systole, appearing as a "box," and close abruptly at end-systole. The Rv is enlarged. *S*, septum. *Frame 4:* Two-dimensional echocardiogram (left apical long axis view) recorded 2 days after frames 1–3. Pleural effusion *(PlF)* has developed. The main pulmonary artery *(PA)* is dilated. Heartworms *(arrow)* are present in the right atrium *(RA)*. (Courtesy of Dr. N. Sydney Moïse.)

serious concomitant problems, such as hepatic insufficiency, renal failure, or the nephrotic syndrome, are not particularly good candidates for adulticidal therapy. Also, the treatment of some very old dogs may not be appropriate, particularly if the patient has class 1 or 2 disease and the infection is not life-limiting.

Arsenical drugs with adulticidal properties include thiacetarsamide (shortcomings include a narrow therapeutic index, lack of efficacy against young female heartworms, and the requirement for—and hazards of—intravenous administration), and melarsomine dihydrochloride (good efficacy against immature and young adult heartworms which are the least sensitive to thiacetarsamide).[62, 63] Every dog should be carefully evaluated prior to initiating therapy and re-evaluated prior to each injection. Anorexia, persistent vomiting, and icterus are indications to abort arsenical therapy. Such complications are rarely encountered with melarsomine but can be expected in up to 20 percent of dogs receiving thiacetarsamide.[64, 65]

No clinical pathologic abnormality is predictive of acute arsenic toxicity in overtly healthy dogs. Routine monitoring of serum liver enzymes during therapy is not helpful, as serum levels of the hepatic enzymes often rise in dogs that tolerate treatment without other adverse sequelae.[40, 41] Contraindications to arsenical therapy in dogs include hepatic insufficiency (indicated by hypoalbuminemia, moderately to severely abnormal liver function tests, biopsy-confirmed severe hepatic fibrosis, and icterus.

MELARSOMINE DIHYDROCHLORIDE

Melarsomine dihydrochloride (Immiticide, Rhone Merieux) is an organic arsenical. Unlike thiacetarsamide, it is highly effective against all ages and both sexes of adult *D. immitis*.[62, 63, 66–69] Prospective clinical trials in Europe and the United States[40, 66, 67, 70, 71] have demonstrated melarsomine's efficacy in dogs with mild to moderately severe heartworm disease.

For standard therapy, melarsomine is administered at a dosage of 2.5 mg/kg by deep intramuscular injection into the epaxial lumbar musculature, and it is given as two injections at a 24-hour interval.[66] During injection, care must be taken not to deposit the drug in the tract as the needle is withdrawn.[66] The needle should be withdrawn quickly and digital pressure applied over the injection site for 1 minute. These two injections eliminate adult worms in approximately 75 percent of infected dogs, and seroconversion occurs in up to 90 percent of all dogs by 8 months after the initial treatment.[67] Four months following initial therapy, two additional injections can be given at a 24-hour interval to eradicate any remaining worms.[66]

A modified protocol for treating class 3 dogs and

class 2 dogs with high worm burdens consists of a single initial injection (2.5 mg/kg), followed in 1 month by two injections at a 24-hour interval. Approximately 50 percent of the worms are killed by the reduced initial dosage regimen, therefore diminishing the severity of postadulticide thromboembolic complications. One to several months later, when the pulmonary response to the initial treatment has subsided, a second course of therapy is given to eliminate remaining worms.

Adverse effects are usually mild, consisting of tenderness and mild swelling at the injection site. Some dogs have a reduced appetite for 1 to 2 days. More pronounced lameness and damage to the sciatic nerve can result if melarsomine is injected into the hind leg. Systemic side effects are rarely serious enough to warrant interruption of treatment. However, dogs overdosed with twice the recommended dose of melarsomine show obvious distress, salivation, tachycardia, tachypnea, colic, restlessness, and apprehension within several hours of administration, followed by shock. Toxic reactions to melarsomine are treated using British antilewisite (BAL), 3.0 mg/kg administered two or three times 3 hours apart. Although melarsomine is a more effective adulticide than thiacetarsemide, the severity of post-treatment pulmonary thromboembolism in dogs treated with melarsomine is reportedly no worse than that observed with thiacetarsamide.[68] All factors considered, the therapeutic index of melarsomine is superior to that of thiacetarsamide sodium.

THIACETARSAMIDE

Thiacetarsamide (Caparsolate, Sanofi) is sufficiently stable in aqueous solution for storage in multiple dose vials. It deteriorates when exposed to light, room temperature, or air, resulting in a yellow-orange discoloration or precipitation.

Its mechanism of action is not certain, but there is a direct relationship between blood arsenic concentrations and adulticide efficacy. Half-life is approximately 45 minutes, and more than 80 percent of the drug is eliminated during the first 48 hours after injection.[65] Peak concentrations of arsenic are similar following each injection, but the postdistribution concentration rises with each dose. Tissue concentrations are highest in the liver and kidneys. Low blood concentrations persist for up to 12 days after standard treatment.

The most important determinant of efficacy is the duration of worm exposure to the minimum effective concentration of arsenic. Worm kill appears to be less in dogs that metabolize and/or excrete thiacetarsamide rapidly than in dogs that eliminate thiacetarsemide more slowly.

Thiacetarsemide's steep dose-response curve and narrow therapeutic index produce variable efficacy and frequent toxicity.[72–76] The standard treatment regimen is 2.2 mg/kg (0.22 ml/kg) given as four intravenous injections over a 2-day period. It is important that the interval between injections does not exceed 12 hours. Each injection should be given into a peripheral vein as distally as is feasible. Under no circumstances should thiacetarsamide be injected unless there is 100 percent certainty of proper vein cannulation. To facilitate injections, we use a butterfly (scalp) needle and a two-syringe technique. After cannulation of the vein, a suitable solution is injected in sufficient volume to ensure that extravasation does not occur. The flushing syringe is detached, the thiacetarsamide-containing syringe is attached, and the injection is made over a period of 15 to 30 seconds. Multiple injections at the same site are not recommended. Some clinicians prefer to use indwelling catheters and report no complications. If an indwelling catheter is employed, a flushing solution should be injected prior to each treatment to ensure that extravasation of thiacetarsamide does not occur.

Extravasation of thiacetarsamide produces pain, heat, and swelling within an hour. Topical DMSO (dimethyl sulfoxide) or a DMSO-soluble corticosteroid mixture should be applied several times daily for several days. This treatment usually reduces tissue necrosis.

An important limitation is that immature worms, especially females, are not very sensitive to the drug.[63, 65, 74–76] Essentially 100 percent of male heartworms aged 2, 6, 12, and 24 months are killed using the standard thiacetarsamide treatment protocol. By comparison, about 40 to 66 percent of the female worms 4 to 12 months old are killed.[76] Increasing the dosage by as much as 33 percent per injection increases the percentage of heartworms killed,[75] but the risks of toxic reactions and postadulticidal pulmonary thromboembolic disease are also increased.[59] Increasing the total number of injections to six given over a 3-day period does not improve the percent of heartworms killed.[75, 77] Despite survival of some heartworms, thiacetarsamide treatment usually results in improvement in clinical signs and partial resolution of pulmonary vascular disease.

When microfilaremia persists following administration of thiacetarsamide and two microfilaricidal doses of ivermectin, it is likely that some adult worms have survived. Several therapeutic options are available. One may repeat the standard thiacetarsamide treatment regimen immediately, but since most resistant infections are due to young female worms, immediate retreatment may not be successful. Increasing the dosage of thiacetarsamide by 10 to 20 percent improves worm kill but also increases the risk of toxicity.[77] A preferable alternative is to place these dogs on macrolide prophylaxis and perform an antigen test 3 months post-thiacetarsamide. If the antigen test is positive,

adulticide treatment failure is confirmed, and retreatment with thiacetarsemide or melarsomine can be considered. This decision to retreat depends on the severity of the initial disease, the degree of clinical improvement observed, and the dog's age, health status, and working requirements. Quantitative or semiquantitative antigen-detecting assays may be helpful. If retreatment with thiacetarsemide is elected, we prefer to wait 6 to 12 months to ensure that the young worms have matured and become more sensitive to the drug. If owners elect not to retreat, the dog should be placed on heartworm prophylaxis with ivermectin. Periodic monitoring of thoracic radiographs is also prudent.

DISCONTINUATION OF THIACETARSAMIDE TREATMENT

Adulticidal therapy should be discontinued in the face of impending toxicity. Treatment delay of 1 to several months is rarely of consequence. The principal indication to abort organic arsenical treatment is acute hepatic toxicity. This is recorded in up to 20 percent of dogs receiving thiacetarsamide[65] and occurs most often after the first injection. This reaction is uncommon with administration of melarsomine.

Protracted, repetitive vomiting and persistent anorexia are the principal clinical signs of toxicity. Icterus is an uncommon but serious complication that may lead to death. Inadequate pretreatment evaluation or inadequate patient observation increases the risk and severity of acute toxicity. Although thiacetarsemide reactions can be serious, there have been no deaths associated with organic arsenical toxicity in our practice during the past 18 years.

When acute toxicity necessitates discontinuation of treatment, supportive care is provided. The pet should be discharged only when hydration is adequate, appetite has returned, and renal function is normal. Restriction of activity and a high-carbohydrate, low-fat diet are prescribed. There is no proven benefit from "liver-sparing drugs" containing methionine, choline, and inositol. The entire treatment regimen is repeated 4 to 6 weeks later, at which time acute toxicity is seldom encountered. Nearly all dogs that have had an initial adverse reaction tolerate a second course of thiacetarsamide.

ANCILLARY DRUG THERAPY

HEPARIN

Heparin is often used to treat symptomatic pulmonary thromboembolism (PTE) following adulticide therapy, or to prevent PTE in dogs with severe pulmonary arterial disease.[77, 78] Pulmonary thromboembolism is a common complication of heartworm therapy (see Figs. 30–4, 30–6, 30–7). It is most frequently seen 5 to 21 days postadulticidal treatment. On occasion, PTE occurs spontaneously. Clinical signs of PTE include depression, fever, anorexia, respiratory distress, coughing, epistaxis, hemoptysis, pale mucous membranes, tachycardia, and weak pulses. An inflammatory leukogram, thrombocytopenia, and mildly prolonged activated clotting time are common laboratory abnormalities in dogs with PTE. Heparin administration (75 to 150 IU/kg, SQ, tid) frequently produces clinical improvement within 24 to 48 hours. The dose should be adjusted to prolong the activated partial thromboplastin time (aPTT) 1.5 to 2 times normal. Heparin therapy is continued for 5 to 21 days, with withdrawal being gradual over several days. Dogs experiencing PTE prior to treatment with an adulticide are at increased risk for a recurrent episode following adulticidal therapy.

Low-dose calcium heparin, 50 to 100 IU/kg, subcutaneously three times daily, has also been successfully used to reduce the severity of postadulticidal thromboembolic complications in dogs with severe pulmonary arterial disease.[78] It is begun 1 to 2 weeks prior to and is continued for 4 to 6 weeks after adulticidal treatment. Such therapy is not completely effective, but postadulticide mortality is reduced compared with dogs treated with aspirin or indobufen.[78]

ASPIRIN

We do not recommend aspirin for the treatment of asymptomatic dogs. Aspirin has been used prophylactically to reduce the severity of laboratory-induced pulmonary arterial disease and to treat spontaneously occurring severe pulmonary arterial disease[40, 41, 59, 60, 79–86] (see Figure 30–8). Aspirin is administered for 1 to several weeks (5–7 mg/kg, daily) prior to and during treatment, and for several weeks postadulticide. By inhibiting platelet adhesion and activation, myointimal proliferation is reduced.

Clinically, aspirin has been combined with protracted cage confinement. Thus, it can be argued that cage rest alone may be responsible for improved survival. Aspirin and cage confinement for severe heartworm disease do not totally eliminate thromboembolic complications. Treatment success may require careful patient monitoring and supportive care, heparin, and corticosteroids.[41]

CORTICOSTEROIDS

Corticosteroids have been successfully used to treat heartworm-infected dogs with eosinophilic pneumoni-

tis, pulmonary infiltrates, and eosinophilic granulomas developing prior to and after adulticide therapy.[59, 60, 84, 86] In the former two circumstances, prednisone (1.0 mg/kg daily) is administered until there is clinical and radiographic evidence of improvement.

The indications for and routine use of corticosteroids in heartworm-infected dogs need to be critically re-evaluated. Routine prophylactic administration is not recommended. Corticosteroids are procoagulant and can reduce pulmonary blood flow when administered for several weeks. In addition, corticosteroid administration during and immediately following thiacetarsamide can decrease worm kill.

TREATMENT MODIFICATIONS WITH SEVERE HEARTWORM DISEASE

Heartworm-infected dogs with more advanced pulmonary arterial disease and/or high worm burdens are challenging to treat. Mortality of 50 to 60 percent has been reported in such animals that receive standard treatment with thiacetarsemide.[40, 41] Dogs with class 3 disease typically show loss of vigor, exercise intolerance, syncope, persistent or severe coughing, and/or signs of right-sided congestive heart failure.[40–42] They tend to be older than dogs with class 1 and 2 disease and are more likely to have an occult infection.[67] The worm burden is variable in class 3 dogs, but on average, it may be lower than that observed in class 2.[67] Radiographic findings in class 3 dogs include marked enlargement of the main pulmonary artery segment and lobar pulmonary arteries, as well as tortuosity and blunting of the peripheral arteries (see Fig. 30–8). Parenchymal lung infiltrates are also frequently present. Class 2 dogs with high worm burdens are identified when large numbers of worms are imaged by echocardiography, or by serologic detection of high circulating heartworm antigen concentration. To improve survival, four alternative protocols have been devised:

HEARTWORM EXTRACTION

When severe heartworm disease is associated with a high worm burden, most of the worms can be extracted from the right heart and pulmonary arteries utilizing a long, flexible alligator forceps with fluoroscopic guidance.[39] The procedure is performed under anesthesia, which is generally tolerated with few complications. Either jugular vein is surgically isolated and the forceps is introduced via venotomy and manipulated into the heart and pulmonary arteries. The jaws of the forceps are opened, advanced slightly, closed, and the forceps are withdrawn, hopefully with 1 to several worms. The procedure is repeated until several passages fail to retrieve worms.

If all the worms are removed, additional treatment is not needed. Otherwise, adulticide therapy is administered several weeks after clinical improvement has occurred. In any case, an antigen-detecting serologic test is indicated in 3 months to determine whether any heartworms remain.

STAGED TREATMENT WITH MELARSOMINE

Modification of the standard melarsomine protocol to accomplish a staged reduction in heartworm numbers has been a successful alternative protocol.[42, 66] Initially, only one dose of melarsomine (2.5 mg/kg), rather than two, is administered.[42, 66] After 1 month of restricted activity, thromboembolic complications, which are usually mild, will have subsided. The remaining worms are then killed using the standard dosage (two intramuscular injections, 2.5 mg/kg, given at a 24-hour interval). This same method has been recommended for dogs with class 2 disease and a large worm burden.[61a] Using this strategy, the initial worm kill is limited, as is the severity of postadulticide thromboembolic lung complications. Survival of greater than 90 percent has been reported using this modified melarsomine dosage schedule.[67]

Additional restriction of activity is recommended for at least 1 month. Microfilaricidal therapy is provided, if appropriate, 4 to 6 weeks after the second course of melarsomine therapy. Reinfection during the treatment period is not usually a problem since melarsomine will kill most of the migrating larvae. A heartworm antigen test is performed 3 months after the second course of melarsomine to ensure that worm eradication has been achieved.

ASPIRIN AND CAGE REST

A third approach is to reduce platelet function with aspirin (5 to 7 mg/kg once daily) and restrict exercise prior to thiacetarsamide therapy.[40, 41] Approximately 80 percent survival has been achieved with this regimen, compared with 40 to 50 percent survival with standard thiacetarsemide treatment. Aspirin reduces the severity of pulmonary arterial disease, thus improving blood flow. We always combine aspirin treatment with strict cage confinement. This reduces demands on the right side of the heart by eliminating the need to expel large stroke volumes through a poorly compliant pulmonary arterial system, thereby reducing pulmonary artery

pressure. Severe exercise restriction reduces the complications of thiacetarsemide therapy and contributes to improved survival. Some argue that similar results might be achieved with restricted activity alone, coupled with thiacetarsamide treatment.

Aspirin and cage confinement are continued for 3 weeks prior to treatment, during treatment, and for 3 weeks thereafter. This protocol is time-consuming, intensive, and expensive. Thromboembolic complications often occur prior to or following thiacetarsamide therapy. Strict patient monitoring of clinical status, blood count, and platelet count is required. Appropriate supportive therapy (usually heparin) is provided when complications arise.

LONG-TERM LOW-DOSE HEPARIN

A fourth approach to the treatment of class 3 dogs is the prophylactic use of heparin to reduce pulmonary thromboembolism. Calcium heparin (50 or 100 IU/kg SC tid) was administered to heartworm-infected dogs.[42] Survival was 97.5 percent in heparin-treated dogs, compared with 73.5 percent in dogs treated with antiplatelet drugs. Postadulticide complications were reduced more than with aspirin therapy. We have used heparin sodium (75 IU/kg SC tid) 1 to 2 weeks prior to adulticidal treatment, continued during the 2 days of adulticide treatment, and extended for 3 weeks post-therapy. Strict cage confinement is recommended.

The relative merits of anti-inflammatory drugs (aspirin) and anticoagulants (heparin) for treating or preventing treatment complications are controversial. When aspirin treatment is started concurrently with thiacetarsamide, the severity of arterial disease is reduced and the impairment of blood flow is lessened.[79–82] However, in a large prospective study, low-dose calcium heparin reduced postadulticide complications more than aspirin.[78] Other investigators have been unable to substantiate the benefits of aspirin or thrombolytic drugs.[87, 88] Neither aspirin nor a variety of vasodilating and thrombolytic drugs significantly reduced pulmonary arterial pressure following the injection of heartworm segments and autologous blood clots.[87] Luethy and coworkers[88] compared the severity of thromboembolic disease in three groups of dogs following adulticide treatment. One group was treated with aspirin (15 to 22 mg/kg daily), one with heparin (sufficient to produce a 1.5 to 2 times increase in clotting times), and one group served as controls. Both treatment groups had lower angiographic scores for severity of pulmonary vascular obstructions, but neither was significantly less than the untreated control dogs.

The aforementioned treatment modifications do not ensure a successful outcome and do not negate the necessity of close patient observation, careful monitoring, attention to detail, and appropriate ancillary treatment.

CHRONIC COR PULMONALE WITH ABSENT OR LOW WORM BURDEN

Some dogs present with clinical signs of severe cor pulmonale without circulating microfilariae and a weak or negative antigen test, indicating either a low worm burden or the absence of adult heartworms. They exhibit exercise intolerance, syncope, or signs of right-sided CHF. They may have a history of prior heartworm treatment or chronic heartworm infection without treatment, or no prior diagnosis of heartworm infection. Thoracic radiographic changes are consistent with severe pulmonary hypertension. These include enlargement of the main pulmonary artery segment and lobar pulmonary arteries, and tortuosity and pruning of the more peripheral pulmonary arteries. Echocardiography can confirm pulmonary hypertension, evaluate right heart function, and identify worms. Gross and histologic changes pathognomonic for heartworm disease are present in some but not all affected dogs at necropsy.

Dogs with severe cor pulmonale are difficult to treat successfully. Although adulticidal therapy may be administered when there is evidence of live heartworms (e.g., a weakly positive antigen test), the chronic pathologic changes coupled with low worm burden suggest that improvement is unlikely. Corticosteroids, aspirin, hydralazine, and diltiazem therapy have been used but without significant benefit. Some dogs can survive with severe exercise restriction, particularly if right-sided congestive heart failure is absent.

IMMUNODIAGNOSTIC SEROLOGY TO ASSESS ADULTICIDAL EFFICACY

Heartworm serologic tests now in use are based on antigens associated with mature adult female worms. Live male worms contribute nothing to a positive antigen test result.[48] Antigenemia is usually absent by 12 weeks post-therapy.[89–91] If a weakly positive test result is obtained, an additional antigen test could be done in 1 to 2 months since seroconversion will occasionally occur as late as 5 months postadulticide treatment. Although immunodiagnostic serology is highly sensitive, falsely negative test results can occur if there are less than approximately 1 to 2 adult worms that are younger than 8 months old.[48] This fact may be of little consequence, since persisting low worm burden may

not produce adverse consequences when all adult heartworms have been killed.

If antigenemia persists, whether or not to retreat is debatable. A decision to avoid retreatment can be based on (1) very weak antigenemia, (2) a marked decrease in the strength of the antigen test result as compared with the pretreatment value, (3) mild or absent initial clinical signs, (4) absence of radiographic evidence of pulmonary pathology, (5) marked improvement in clinical and radiographic signs of heartworm disease, (6) a nonworking dog, and (7) serious concomitant problems. Factors favoring retreatment include (1) strong and persistent antigenemia, (2) initially severe clinical and radiographic abnormalities, (3) persistent clinical signs of heartworm disease, (4) a working dog, and (5) no apparent contraindications to retreatment.[91]

HEARTWORM-RELATED CLINICAL SYNDROMES

A number of pathologic sequelae to heartworm infection can be characterized into specific clinical syndromes. They are related to worm burden, host-parasite immune or allergic responses, severity of pulmonary myointimal proliferation, and complications from heartworm death.

EOSINOPHILIC PNEUMONITIS

A hypersensitivity-type pneumonitis develops in approximately 10 to 15 percent of dogs with immune-mediated occult heartworm infections.[92] This syndrome is characterized by pulmonary infiltrates with eosinophilia (PIE) and resembles tropical eosinophilia (pulmonary eosinophilia), a microfilarial disease of human beings.[92–98] Immune-mediated occult heartworm disease results from antibody-dependent leukocyte adhesion to microfilariae and their subsequent entrapment within the pulmonary capillaries.[34, 35] The inflammatory reaction includes neutrophils and eosinophils. The pneumonitis syndrome occurs when a hypersensitivity develops and is characterized by an unusually high number of eosinophils in the inflammatory response.[34, 35]

CLINICAL FINDINGS. Affected dogs experience variable respiratory distress. Clinical signs are usually progressive during a period of a few weeks to 6 months or longer.[92] Coughing and dyspnea are the predominant clinical signs, but severely affected dogs may experience mild cyanosis, anorexia, and weight loss. Bilateral, diffuse "crackles" can be auscultated over the areas of the caudal lung lobes. Characteristic radiographic abnormalities associated with heartworm pneumonitis include diffuse, bilateral, linear interstitial and alveolar pulmonary lung lobe infiltrates (Fig. 30–10). These changes can resemble those of pulmonary blastomycosis and pulmonary edema. Clinical pathology abnormalities include eosinophilia, basophilia, and hyperglobulinemia. Transtracheal lavage cytology typically consists of a sterile, eosinophilic exudate with some nondegenerate neutrophils and macrophages.

THERAPY. Corticosteroid hormone treatment (prednisone or prednisolone, 1 to 2 mg/kg daily, or dexamethasone, 0.2 to 0.4 mg/kg daily) is usually successful. Most dogs experience rapid and complete resolution of clinical and radiographic abnormalities within 3 to 5 days of treatment; some improve within 24 hours. Treatment is usually given orally but may be administered intramuscularly or intravenously to severely affected dogs. Corticosteroid hormone treatment is stopped when there is clinical and radiographic evidence of maximum resolution of pulmonary infiltrates. Thiacetarsamide treatment should be initiated soon thereafter.

PULMONARY GRANULOMAS IN HEARTWORM-INFECTED DOGS

EOSINOPHILIC GRANULOMATOSIS

Eosinophilic pulmonary granulomatosis is a clinical syndrome that is often associated with heartworm infection. It can be confused with primary and metastatic pulmonary neoplasia, systemic mycoses, and lymphomatoid granulomatosis.[99–101] It is important to note that not all histologic diagnoses of eosinophilic granulomatosis represent the same disease, and not all are due to heartworm infection. Eosinophilic granulomas primarily affect the lungs, but approximately 50 percent of necropsied dogs also have eosinophilic infiltration and granulomas in thoracic lymph nodes, trachea, peripheral lymph nodes, liver, spleen, abdominal lymph nodes, small intestine, and kidney. Interalveolar septa are often thickened by fibrous connective tissue, lymphocytes, and plasma cells. Alveoli often contain eosinophilic granular material and some macrophages. Granulomas consist of dense accumulations of large epithelioid cells, macrophages, and eosinophils that obliterate the normal architecture. A few plasma cells, lymphocytes, and mast cells are also present. Areas of necrosis are occasionally observed. Some pulmonary arteries and arterioles are infiltrated by eosinophils. At the periphery of granulomas, alveoli can be identified and are characterized by proliferation of type II pneumocytes with infiltrates of eosinophils and macrophages. A mixed eosinophilic-neutrophilic inflamma-

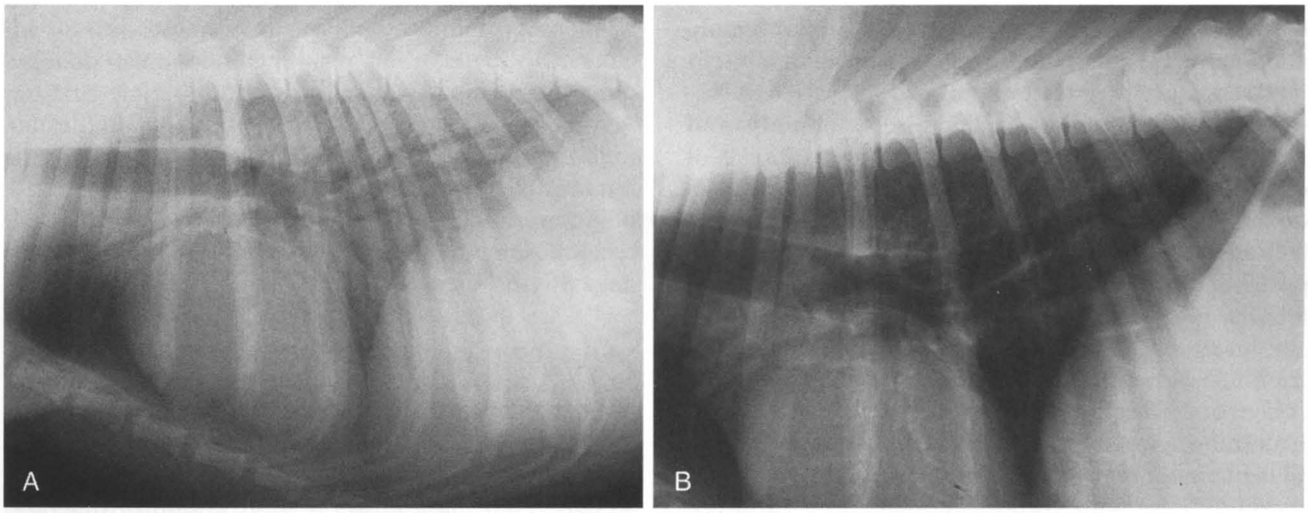


FIGURE 30–10

Lateral radiographs illustrating diffuse, mixed, interstitial, and alveolar infiltrates in the lungs of a dog with occult heartworm disease–associated allergic pneumonitis. Prednisone therapy was administered. Notice the radiographic lung improvement when comparing the pretreatment (A) and post-treatment (B) films.

tion occurs in zones surrounding the granulomas. Bronchial smooth muscle hypertrophy is prominent in granulomatous areas. Perivascular lymphocytic-eosinophilic infiltration is inconsistently associated with small arterioles.

CLINICAL SIGNS. Chronic coughing and dyspnea occur most commonly. Respiratory signs often occur for several weeks prior to presentation, although signs have been present for as long as 12 months in some cases. More severely affected dogs exhibit decreased appetite, weight loss, exercise intolerance, and lethargy. Fever and hemoptysis may occur. This syndrome may develop in dogs with heartworm infections that have been treated as well as untreated. Coughing, dyspnea, and pulmonary crackles are the most common physical abnormalities. Fever, muffled heart and lung sounds, peripheral lymphadenopathy, and weight loss are occasionally detected.

CLINICAL, PATHOLOGICAL, AND RADIOGRAPHIC FINDINGS. Characteristic radiographic findings include (1) multiple pulmonary masses (Fig. 30–11) from 1 to 20 cm in diameter, (2) mixed interstitial-alveolar or interstitial,

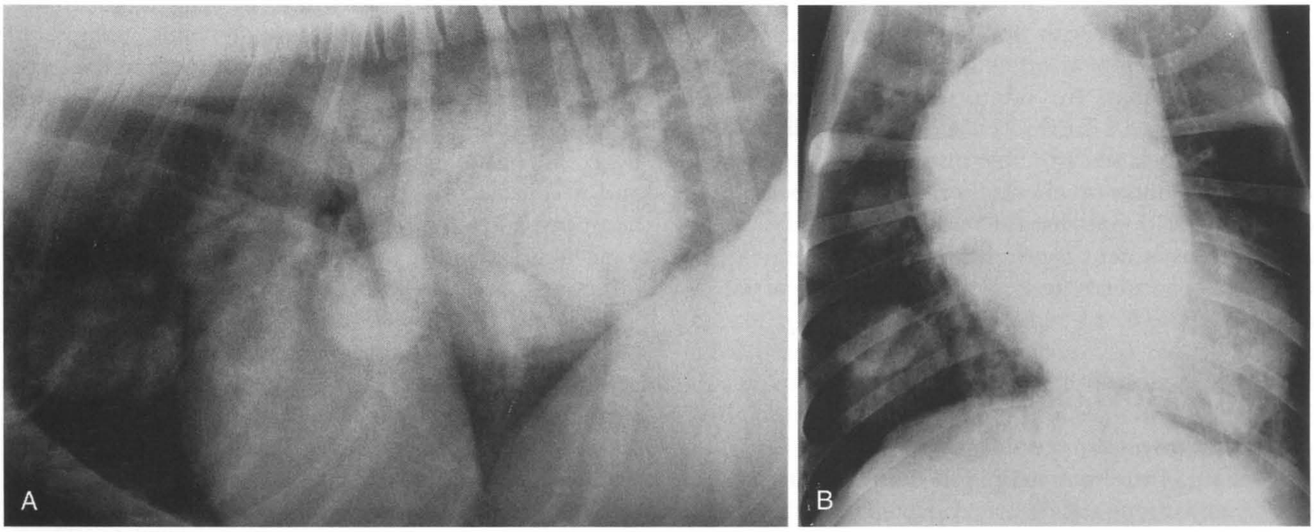


FIGURE 30–11

Lateral (A) and ventrodorsal (B) thoracic radiographs showing multiple pulmonary interstitial nodules of varying size in the lungs of a dog with heartworm disease and eosinophilic granulomatosis.

alveolar, and bronchial lung patterns, (3) hilar lymphadenopathy, (4) pleural effusion, and occasionally, (5) mediastinal or intratracheal masses. Hematologic abnormalities most commonly include eosinophilia and neutrophilia, which are present in up to two thirds of dogs with eosinophilic pulmonary granulomas. Absolute eosinophil counts are often between 1000 and 6000 and can exceed 50,000/μl. Basophilia occurs in approximately 50 percent of affected dogs. Hyperglobulinemia is occasionally present. Transtracheal lavage may yield exudates rich in eosinophils. Pleural effusion, when present, usually contains a high percentage of eosinophils. Peripheral lymphadenopathy is uncommon; when present, fine-needle aspiration yields increased numbers of eosinophils.

MEDICAL THERAPY. Many dogs with eosinophilic pulmonary granulomas respond initially to immunosuppressive and cytotoxic drug therapy. Prednisone (1 to 2 mg/kg orally once daily) produces partial and occasionally complete remission. The latter is more likely with combination therapy such as prednisone plus azathioprine (Imuran, Burroughs Wellcome). Granulomas commonly recur when the dosage is reduced, when the interval between dosages is prolonged, and even when the dosage and interval are not altered. Adulticide treatment is administered after significant reduction of lung pathology and improvement of clinical signs has been accomplished. Disease progression or relapse occurs in most cases within 1 to 3 months, and additional chemotherapy is usually ineffective.

SURGICAL REMOVAL. Surgical excision of eosinophilic granulomas has had limited application. At surgery, multiple small granulomas not visualized by radiography are usually present. Even when lung lobectomy is performed in dogs with apparently localized disease, lesions can develop in other lobes. Dogs with eosinophilic granulomas are often poor anesthetic risks. Nonetheless, given the limited success of medical therapy, lobectomy is a reasonable option when the disease is localized. Follow-up chemotherapy should be administered if additional disease is discovered at surgery. Adulticide treatment is administered after surgical recovery when antigen tests indicate heartworm infection.

LYMPHOMATOID GRANULOMATOSIS

Pulmonary lymphomatoid granulomatosis is a rare pleomorphic lymphoid neoplasm that can affect dogs of all ages without sex or breed predilection.[102] About 20 canine cases have been reported, 3 of which had been previously treated for heartworms. Gross lesions consist of solitary or multiple, firm, nodular pulmonary masses. Histologic examination shows infiltration by pleomorphic mononuclear cells, often with an angiocentric pattern and resulting in vascular obliteration.[102] Historical, clinical, and radiographic findings are very similar to those described in dogs with eosinophilic granulomatosis. Surgical excision or biopsy is required to distinguish lymphomatoid from eosinophilic granulomas. Treatment with prednisolone and cyclophosphamide has been recommended.[102] Many dogs do not respond.

CAVAL SYNDROME

This develops when large numbers of worms (from 50 to > 200) mature over a short period of time and localize in the cranial and caudal vena cavae and right atrium.[103–110] Caval syndrome is virtually absent in areas of low heartworm incidence, but is common in some highly endemic regions along the Gulf Coast. Most cases occur in spring and early summer in male dogs that spend most of their time outdoors. These infections probably represent a massive exposure to infective larvae during the previous summer and early fall. Caval syndrome is associated with marked pulmonary hypertension and mechanical interference with tricuspid valve closure, leading to tricuspid regurgitation and elevated central venous pressure.[107]

CLINICAL FINDINGS. Clinical signs result from cardiogenic shock, intravascular hemolysis, and hepatic and renal failure. Hemolysis is caused by erythrocyte trauma from worms and fibrin deposition within the vena cavae and right side of the heart.[107–110] Increased erythrocyte fragility results from alterations in serum-free and esterified cholesterol concentrations and lecithin acyltransferase activity.

Caval syndrome is recognized by acute collapse in high-risk dogs displaying tachypnea, tachycardia, pale mucous membranes, weak and thready pulses, hemoglobinemia, hemoglobinuria, a gallop heart rhythm, a heart murmur, jugular vein distention or pulsation, and a split second heart sound. Ascites, icterus, and hemoptysis are less common findings. Clinical pathologic abnormalities include regenerative anemia, an inflammatory leukogram, eosinophilia, and increased hepatic enzyme activity. Most affected dogs have circulating microfilariae. Azotemia, hemoglobinuria, and proteinuria are also common. It is important to test for coagulation abnormalities. Disseminated intravascular coagulation is suggested by thrombocytopenia, prolonged activated clotting time, hypofibrinogenemia, and increased fibrin degradation products.[105, 106, 109]

Radiographic evidence of right sided heart enlargement and enlarged, tortuous pulmonary arteries supports the diagnosis. Common ECG findings include a right axis deviation and tachyarrhythmias.[104, 108, 109]

Echocardiography can confirm the diagnosis by detecting large numbers of heartworms in the venae cavae and right atrium.[108] Indirect evidence of pulmonary hypertension is indicated by enlarged pulmonary arteries, paradoxic septal motion, and right ventricular dilatation and hypertrophy. Left ventricular dimensions may be reduced. Doppler studies can document tricuspid and pulmonic insufficiency and pulmonary hypertension.

THERAPY. The only effective treatment is prompt extraction of as many worms as possible from the venae cavae and right atrium as soon as the syndrome is recognized.[103] Most dogs are in shock. Chemical restraint should be minimal, and local anesthesia is preferred. To support blood pressure and cardiac output, fluid therapy may be needed during worm extraction.

A technique for worm removal has been described.[103] With the dog positioned in left lateral recumbency, the right jugular vein is isolated and ligated cranially, and the ligature is used to elevate the vein while a venotomy is performed. A long, small-diameter alligator forceps is passed into the jugular vein to the approximate location of the heart base. Extension of the neck is often required when a rigid forceps is employed. Perforation of the vena cava or right atrium can occur unless gentle instrument handling is practiced. The instrument jaws are opened and the forceps advanced slightly; the jaws are then closed and the forceps retracted, removing worms with each passage. The process is repeated until five or six successive attempts fail to extract a worm. Successful treatment is associated with removal of at least 50 worms. Judicious fluid therapy and other supportive measures are maintained following surgery. Clinical and hematologic improvement occurs rapidly in successfully treated dogs. Adulticide therapy is administered several weeks following surgery, depending on the rate and degree of postsurgical improvement.

POSTADULTICIDE PULMONARY THROMBOEMBOLISM

Adulticide therapy is the most important recognized cause of acute pulmonary thromboembolism (PTE) in dogs.

CLINICAL FINDINGS. Clinical signs of PTE include coughing, dyspnea, fever, hemoptysis, weakness, lethargy, pulmonary crackles, and pale mucous membranes. Thoracic radiographs of dogs with heartworm-associated PTE usually reveal marked enlargement of the lobar arteries with parenchymal pulmonary infiltrates[40, 41] (Fig. 30–7). These infiltrates are patchy or hazy, tend to be most severe adjacent to the caudal or intermediate lobar arteries, and may produce partial or complete lung lobe consolidation. Severe thrombocytopenia and an inflammatory leukogram or mature neutrophilia are often present.

THERAPY. Thrombolytic drugs are expensive, and they have not been critically evaluated in dogs with heartworm-associated PTE. Heparin is used in most cases to limit further thrombosis.[78, 81] We use 75 IU/kg subcutaneously every 8 hours, which is continued until the platelet count is normal. This usually necessitates approximately 5 to 7 days of heparin therapy, although up to 3 weeks of treatment is required in some dogs. Others advocate a higher heparin dosage (100–200 IU/kg every 6–8 hours), which is adjusted to achieve a 1.5 to 2-fold increase in clotting time (aPTT). Oxygen administration by cage or an intranasal oxygen line (50 to 100 ml/kg/min) is also recommended.[30] Oxygen reduces pulmonary arterial pressures and improves perfusion.[111]

Response to therapy is usually rapid. Clinical improvement, increased platelet count, and improved blood gas values may occur within 24 to 48 hours. Hemoglobinemia and hemoglobinuria usually resolve rapidly. Strict cage confinement is necessary for at least 3 weeks.

We often prescribe corticosteroids (prednisone, 1.0 mg/kg daily) in dogs with PTE. Whereas short-term administration (3 to 5 days) is probably not harmful, extensive use is not recommended since corticosteroids are procoagulant and reduce pulmonary blood flow.[59, 60, 83]

We usually continue aspirin therapy in dogs with severe (Class 3) heartworm disease unless there is evidence of gastrointestinal bleeding such as hematemesis, decreasing hematocrit, or melena. Melena is not, however, an early or sensitive indicator of intestinal bleeding.

MICROFILARICIDAL THERAPY

IVERMECTIN

All dogs with circulating microfilariae should receive microfilaricidal treatment within 4 to 6 weeks of adulticidal therapy. Although not approved by the FDA for this purpose, ivermectin is the most practical, effective, and commonly used agent. To eliminate microfilariae, ivermectin is administered as a single oral dose (50 μg/kg) in the morning. The dog is observed in the hospital for adverse reactions during the day and is discharged in the afternoon.[112, 113] Either the equine product Eqvalan (Merial) or the cattle product Ivomec (Merial) can be administered. Both drugs are generally diluted 1:9 (the former with water for immediate use

and the latter with propylene glycol for extended shelf life), and administered at a dosage of 1 ml per 20 kg orally. Ivermectin rapidly kills microfilariae and eradicates them in at least 90 percent of dogs by 21 days post-treatment.[114] Most microfilariae are killed within hours of ivermectin administration.

ADVERSE EFFECTS

Adverse reactions occur in less than 10 percent of dogs.[112, 115] The prevalence and severity of adverse reactions are related to high microfilarial counts (> 10,000/ml). Reactions begin within several hours and usually consist of lethargy, vomiting, and occasionally diarrhea, which are self-limiting. Severe reactions, which may be life-threatening, are manifested by tachycardia, tachypnea, weakness, pale mucous membranes, and decreased blood pressure. These are uncommon and may be effectively treated with soluble (rapid-acting) corticosteroid preparations and intravenous crystalloid fluid administration. Death from such reactions is rare and is usually attributable to late recognition and/or inadequate therapy. Some dogs with high microfilarial concentrations may experience mild lethargy and anorexia for 1 to 2 days after ivermectin administration.

Ivermectin at a dosage of 50 μg/kg appears to be safe for administration to collie and collie-type dogs.[116, 117] We are unaware of adverse reactions at dosages under 100 μg/kg. Severe, life-threatening reactions reported in a subset of collies have occurred at dosages of greater than 200 μg/kg and were characterized by acute ataxia, mydriasis, weakness, seizures, coma, and high mortality.[116] Recovery requires several weeks and intensive care.

CONFIRMATION OF EFFICACY

Most microfilariae are killed within 24 hours of a single dose of ivermectin. However, a few microfilariae may survive up to 3 weeks post-treatment. Consequently, a microfilarial concentration test should be performed 3 weeks post-treatment.[116, 117] If negative, a prophylactic regimen is instituted. If positive, the ivermectin protocol should be repeated. If microfilariae persist 3 weeks after a second administration, adulticide failure should be considered.

MILBEMYCIN OXIME

Milbemycin oxime (Interceptor, Ciba-Geigy) is microfilaricidal at the prophylactic dosage of 0.5 to 1.0 mg/kg.[118] Some clinicians routinely prescribe Interceptor for microfilaricidal use, for which it is highly effective. In general, the risk and type of adverse reactions are similar to those associated with ivermectin at its microfilaricidal dosage (50 μg/kg).[118] Neither Ciba-Geigy nor Merck and Company recommend or support off-label use of their products.

Because there is a risk of adverse reactions following microfilaricide treatment, some advocate that acute microfilaricide treatment not be administered. Rather, ivermectin treatment should be administered (e.g., Heartgard or Heartgard-30 Plus, Merial) soon after adulticidal treatment. The microfilariae will disappear over the next several months. Until that time, however, such dogs serve as reservoirs.

Heartworm Prophylaxis

Heartworm prophylaxis is recommended for all dogs at risk of infection. In general, it is recommended year-round in tropical and subtropical climates. One study has demonstrated that little or no transmission occurs in the southeastern United States during the coldest months of the year, like December and January.[119] Preventive medication is usually begun when the average daily temperature exceeds approximately 58° F.[120] Some clinicians recommend year-round prophylaxis to improve owner compliance.

Heartworm testing is an integral component of prophylactic therapy. All dogs placed on heartworm prophylaxis for the first time should be both microfilariae- and antigen-free.[117] All dogs that will receive diethylcarbamazine products must have a negative microfilarial concentration test prior to drug initiation and at least annually thereafter.[117] We recommend annual antigen testing in all dogs regardless of the type of heartworm prophylaxis used. Although some have questioned the need for annual testing in dogs taking monthly preventives, poor client compliance is a reality that cannot be ignored. Failure to properly increase the drug dosage in large, rapidly growing puppies may also cause prophylactic failure.

The choice of prophylactic drug is influenced by two characteristics of the available products: (1) daily versus monthly administration, and (2) concomitant control of intestinal helminths.

DAILY PROPHYLAXIS USING DIETHYLCARBAMAZINE

Diethylcarbamazine (DEC) has stood the test of time, is safe, and is highly efficacious. Since it kills *D. immitis* larvae at the L_3–L_4 molt stage, this narrow window of opportunity necessitates daily administration. DEC is available in tablets, chewable tablets, and liquid; it is dosed at 6.6 mg/kg. Dogs must be microfilariae-free when DEC is initiated. Acute, potentially

life-threatening adverse reactions are likely (15 to 85%) when DEC is administered to microfilaremic dogs.[121-123] Although dogs with less than 50 microfilariae/ml of peripheral blood seldom react, microfilarial concentrations are rarely determined in clinical practice. Nondose-dependent lethargy and gastrointestinal reactions are seen within approximately 1 hour of administration. Vomiting, defecation, and diarrhea may occur. Bradycardia, signs of reduced cardiac output, and peripheral blood pressure may develop. Some affected dogs then become very weak, salivate, and develop shock.[124] Dogs surviving less severe reactions experience recurrence with each dosage, and subsequent reactions tend to exacerbate. These reactions are related to the presence of microfilariae and gravid female worms. If a dog receiving DEC is found to be microfilaremic, continued daily use may not produce adverse reactions. However, should DEC administration be stopped for as few as 4 days or longer, reinstitution can result in the aforementioned reaction.[122-124]

Extended parasite control is provided by the addition of oxibendazole (Filarabits Plus, Norden Laboratories) to control roundworms, hookworms, and whipworms as well as heartworms.[125] Although this drug is highly popular and efficacious, hepatotoxicity has been uncommonly associated with its use. Toxicity is characterized by increased serum hepatic enzyme activity and, in some cases, abnormal hepatic function tests; it is usually self-limiting once the drug is withdrawn.

MONTHLY PROPHYLAXIS USING MACROLIDE ANTIBIOTICS

A number of macrolide antibiotic drugs are available for heartworm prophylaxis, with some providing extended parasite control.[125, 129] They are very effective when administered monthly, since larvae up to 2 months of age are readily killed by these agents. The monthly use of these drugs causes gradual disappearance of circulating microfilariae in dogs with adult heartworms. This may be due to the effect of macrolides on the male worm reproductive capacity.[126-128] Amicrofilaremic infections also develop in dogs that are placed on macrolides more than 4 months after being inoculated by infected mosquitoes. Thus, antigen-detecting serologic tests should be used for annual screening. It is also prudent to use serologic tests whenever heartworm prophylaxis is initiated more than several months into the "season." An antigen test should be performed 6 to 8 months after monthly prophylaxis is initiated and then annually thereafter.

IVERMECTIN

Ivermectin (and Heartgard-30 Plus, Merial) is a highly effective macrolide prophylactic drug when administered at a monthly dosage of 6 to 12 μg/kg. At this dose, Heartgard can be safely administered in the face of circulating microfilariae. At a dosage of 50 μg/kg, ivermectin's antilarval action can be extended to 3 months postinoculation of L_3, with approximately 90 percent efficacy.[31] Administration of this high dosage can be considered when a monthly dosage has been missed.

Currently, ivermectin is the drug of choice to prevent superinfection in dogs with persisting adult worms and microfilariae and it has a "reach back" effect when it is used at prophylactic doses for 1 year.[130, 130a] The monthly prophylactic dosage (6 μg/kg) of Heartgard-30 is highly (> 95%) effective in killing young adult worms when treatment is started 4 months after inoculation of L_3 and continued for a year.[130, 130a] In contrast, milbemycin oxime (500 μg/kg), given monthly during the same period, was effective in less than 50 percent of the dogs.

Ivermectin is safe for use in collies at the prophylactic dose, and adverse reaction effects of any type are uncommon in all dogs.[116, 117] Heartgard-30 Plus (ivermectin plus pyrantel pamoate) provides a broader spectrum of control to include roundworms and hookworms while maintaining the convenience of monthly administration for heartworm prevention.[128, 129]

MILBEMYCIN

Milbemycin oxime (Interceptor, Ciba-Geigy) is a highly effective, monthly macrolide prophylactic that also controls roundworm, hookworm, and whipworm infections.[131-133] The drug is safe in collies,[132] but it is not recommended for dogs with circulating microfilariae, since the prophylactic dosage (0.5 to 1.0 mg/kg) is also microfilaricidal. The resulting adverse reactions are similar to those described in some dogs receiving ivermectin at the microfilaricidal dosage.

MOXIDECTIN

Moxidectin (American Cyanamid) is a highly effective, safe, macrolide prophylactic drug administered monthly at a dosage of 3.0 μg/kg.[134-139] It is safe for administration to collies[138] and can be given to microfilaremic dogs without fear of reaction, since it is not microfilaricidal at this dosage.[139]

REFERENCES

1. Heartworm Infection Incidence Map 1986. Proceedings, Heartworm Symposium, Washington, D.C., American Heartworm Society, 1986, inside cover
2. Rawlings CA. Heartworm Disease in Dogs and Cats. Philadelphia, WB Saunders, 1986

3. Lewis RE, Losonsky JM. Sex and age distribution of dogs with heartworm disease. *In* Otto GF (ed): Proceedings, Heartworm Symposium, 1977. Bonner Springs, KS, Veterinary Medical Publishing Company, p 8
3a. Walters LL. Risk factors for heartworm infection in northern California; Abstract. Program of the 8th Triennial State of the Heartworm Symposium, 1995, p 16
4. Calvert CA, Rawlings CA. Canine heartworm disease. *In* Kirk RW (ed): Current Veterinary Therapy VII. Philadelphia, WB Saunders, 1983, p 348
5. Scoles GA, Dickson SL. New foci of canine heartworm associated with introduction of new vector species: *Aedes albopictus* in New Orleans and *Ae. sierrensis* in Utah; Abstract. Program of the 8th Triennial State of the Heartworm Symposium, 1995, p 17
6. Genchi C, Di Sacco B, Cancrini G. Role of vectors in the epidemiology of canine and feline heartworm infection in Northern Italy. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 39
7. Orihel TC. Morphology of the larval stages of *Dirofilaria immitis* in dogs. J Parasitol 47:251, 1961
8. Rawlings CA, McCall JW, Lewis RE. The response of the canine's heart and lungs to *Dirofilaria immitis.* J Am Anim Hosp Assoc 14:17, 1978
9. Rawlings CA, Keith JC, Schaub RG. Development and resolution of pulmonary disease in heartworm infection: Illustrated review. J Am Anim Hosp Assoc 17:711, 1981
10. Jackson RF, Keith JC, Schaub RG. Distribution of heartworms in the right side of the heart and adjacent vessels of the dog. J Am Vet Med Assoc 149:515, 1966
10a. Ishihara K, Kitagawa H, Sasaki Y, et al. Changes in cardiopulmonary values after heartworm removal from pulmonary artery using flexible alligator forceps. Jap J Vet Sci 50:731, 1988
11. Schaub RG, Rawlings CA. Pulmonary vascular response during phases of canine heartworm disease: A scanning electron microscopic study. Am J Vet Res 41:1082, 1980
12. Schaub RG, Rawlings CA, Keith JC. Platelet adhesion and myointimal proliferation in canine pulmonary arteries. Am J Pathol 104:13, 1981
13. Keith JC, Schaub RG, Rawlings CA. Early arterial injury-induced myointimal proliferation in canine pulmonary arteries. Vet Res 44:181, 1983
14. Adcock JL. Pulmonary arterial lesions in canine dirofilariasis. Am J Vet Res 22:655, 1961
15. Rawlings CA, Losonsky JM, Schaub RG. Post-adulticide changes in *Dirofilaria immitis*–infected beagles. Am J Vet Res 44:8, 1983
16. Rawlings CA, Lewis RE, McCall JW. Development and resolution of pulmonary arteriographic lesions in heartworm disease. J Am Vet Med Assoc 16:17, 1980
17. Rawlings CA. Cardiopulmonary function in the dog with *Dirofilaria immitis*: During infection and after treatment. Am J Vet Res 41:319, 1980
18. Rawlings CA, Losonsky JM, Lewis RE. Development and resolution of radiographic lesions in canine heartworm disease. J Am Vet Med Assoc 178:1172, 1981
19. Rawlings CA, Keith JC, Lewis RE, et al. Aspirin and prednisolone modification of radiographic changes caused by adulticide treatment in dogs with heartworm infection. J Am Vet Med Assoc 182:131, 1983
20. Otto GF. The significance of microfilaremia in the diagnosis of heartworm infection. *In* Otto GF (ed): Proceedings, Heartworm Symposium, 1977. Atlanta, Veterinary Medicine Publishing Company, 1978, p 22
21. Hinman EH. Studies on the dog heartworm, *Dirofilaria immitis*, with special reference to periodicity. Am J Trop Med 15:371, 1935
22. Carlisle CH. The incidence of *Dirofilaria immitis* in dogs in Queensland. Austral Vet J 45:535, 1969
23. Kume S. Canine Heartworm Disease; A Discussion of the Current Knowledge. Gainesville, FL, University of Florida Press, 1970, p 44
24. Watson AD. A survey of canine filariasis in Sydney. Austral Vet J 49:31, 1973
25. Streitel RH, Stromberg PC, Dubey JP. Prevalence of *Dirofilaria immitis* infections in dogs from a humane shelter in Ohio. J Am Vet Med Assoc 170:720, 1977
26. Jackson RF. A study on the filter technique for the detection and identification of canine microfilariae. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Atlanta, Veterinary Medicine Publishing Company, 1978, p 31
27. Anataphruty M. Studies on chemotherapy of parasitic helminths. Efficacy of ivermectin on the circulating microfilaria and embryonic development in the female worm of *Dirofilaria immitis.* Jap J Parasitol, 31:517, 1982
28. Knight DH, Campbell WC, Weiner DJ, et al. Microfilaricidal efficacy of ivermectin in adulticide treated and untreated heartworm infected dogs. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Washington, D.C., American Heartworm Society, 1986, p 19
29. Rawlings CA, Dawe DL, McCall JW, et al. Four types of occult *Dirofilaria immitis* infection in dogs. J Am Vet Med Assoc 180:1323, 1982
30. Bowman DD, Johnson RH, Ulrich ME, et al. Effects of long-term administration of ivermectin or milbemycin antigenemia in dogs with patent heartworm infections. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 151
31. McCall JW, McTier TL, Supakorndej N, et al. Clinical prophylaxis of experimentally induced infections of *Dirofilaria immitis* by monthly treatment with Heartgard-30[R] beginning at four months PI. Minneapolis, American Association of Veterinary Parasitologists, July 17–20, 1993
32. Knight DH. Heartworm disease. *In* Ettinger SJ (ed): Textbook of Veterinary Internal Medicine. Philadelphia, WB Saunders, 1983, p 1097
33. Wong MM. Studies on microfilaremia in dogs. II. Levels of microfilaremia in relation to immunologic responses of the host. Am J Trop Med Hyg 13:66, 1964
34. Wong MM, Suter PF, Rhode EA. Dirofilariasis without circulating microfilariae: A problem in diagnosis. J Am Vet Med Assoc 163:133, 1973
35. Wong MM. Experimental occult dirofilariasis in dogs with special reference to immunological responses and its relationship to "eosinophilic lung" in man. Southeast Asian J Trop Med Public Hlth 5:480, 1974
36. Lok J, Knight DH, LaPangh DA. Kinetics of *Dirofilaria immitis* microfilaremia regimen of milbemycin oxime. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 143
37. Plue RE, Seward RL, Acre KE, et al. Clearance of *Dirofilaria immitis* microfilaria in dogs using 200 μg/kg ivermectin subcutaneously. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Orlando, FL, Veterinary Medicine Publishing Company, 1983, p 153
38. Rawlings CA, Losonsky JM, Lewis RW. Susceptibility of dogs with heartworm disease to hypoxia. Am J Vet Res 38:1365, 1977
39. Vezzoni A, Genchi C, Raynaud J-P. Adulticide efficacy of melarsomine (RM 340) in dogs with mild and severe natural heartworm infections. *In* Soll MD (ed): Pro-

ceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 231
40. Calvert CA, Thrall DE. Treatment of canine heartworm disease coexisting with right-side heart failure. J Am Vet Med Assoc 180:1201, 1982
41. Calvert CA. Treatment of heartworm disease with associated severe pulmonary arterial disease. *In* Otto GF (ed): Proceedings, Heartworm Symposium. New Orleans, 1986, p 231
42. Ishihara K, Sasaki Y, Kitagawa H. Removal of canine heartworms using flexible alligator forceps. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1989, p 33
42a. Ishihara K, Sasaki Y, Kitagawa H. Clinical and pathological effects of heartworm removal from the pulmonary arteries using flexible alligator forceps. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1989, p 45
43. Courtney CH. Guidelines for the use of parasitologic and serologic screening of heartworm infection. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society. 1992, p 1
44. Tonelli Q. Factors affecting the accuracy of enzyme immunoassays for *Dirofilaria immitis* adult antigen. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Charleston, SC, American Heartworm Society, 1989, p 161
45. Courtney CH, Zeng QY. Applications of heartworm immunodiagnostic tests. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Charleston SC, American Heartworm Society, 1989, p 167
46. Atwell RB, Dixon G. Necropsy-confirmed test results using a whole blood, rapid immunoassay for detection of heartworm antigen. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 11
47. Grieve RB. Advances in the immunodiagnostic diagnosis of *Dirofilaria immitis* infection. Semin Vet Med Surg 2:4, 1987
48. McCall JW, McTier T, Supakorndej N, et al. Further characterization of the sensitivity of several commercially available heartworm antigen test kits. Orlando, FL, North American Veterinary Conference: Veterinary Proceedings. Vol 8, 1994, p 461
49. McCall JW, Supakorndej N, McTier TL, et al. Commercial heartworm antigen test kits detect infections with a single adult female worm but not those with numerous adult male worms only. Minneapolis, American Association of Veterinary Parasitologists, July 17–20, 1993
49a. Hong XQ, Mejia JS, Perler FB, et al. A promising recombinant antigen for the early detection of heartworm infection; Abstract. Program of the 8th Triennial State of the Heartworm Symposium, 1995, p 33
50. Bundesen PG, Martin SA, Dixon GH, et al. An evaluation of the VetRED™ Canine Heartworm Antigen Test. Aust Vet Practit 20:144, 1990
50a. McTier TL, McCall JW, Supakorndej N. Features of heartworm antigen test kits; Abstract. Program of the 8th Triennial State of the Heartworm Symposium, 1995, p 29
51. Di Sacco B, Genchi C, Capelli G, et al. Study of a new serum agglutination test (VetRED[R], AGEN) for the diagnosis of canine cardiopulmonary dirofilariasis (English title). Veterinaria 6:2, 1992
51a. Bland A, McTier T, Freeman KP, et al. Evaluation of the ICT GOLD™ HW heartworm antigen test kit; Abstract. Program of the 8th Triennial State of the Heartworm Symposium, 1995, p 32
52. Rawlings CA, Tonelli Q, Lewis RE, et al. Semiquantitative test for *Dirofilaria immitis* as a predictor of thromboembolic complications associated with heartworm treatment in dogs. Am J Vet Res 54:914, 1993
53. Courtney CH, Zeng Q-Y. The structure of heartworm populations in dogs and cats in Florida. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Charleston, SC, American Heartworm Society, 1989, p 1
54. Calvert CA, Losonsky JM, Brown J. Comparisons of radiographic and electrocardiographic abnormalities in canine heartworm disease. Vet Radiol 27:2, 1986
55. Knight DH. Heartworm disease. Adv Vet Sci Comp Med 1:107, 1977
56. Rawlings CA, Prestwood AK, Beck BB. Eosinophilia and basophilia in *Dirofilaria immitis* and *Dipetalonema reconditum*. J Am Anim Hosp Assoc 16:699, 1980
57. Losonsky JM, Thrall DE, Lewis RE. Thoracic radiographic abnormalities in 200 dogs with spontaneous heartworm infections. Vet Radiol 24:120, 1983
58. Lewis RE, Losonsky JM. The frequency of roentgen signs in heartworm disease. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Atlanta, Veterinary Medicine Publishing Company, 1976, p 73
59. Rawlings CA, Keith JC, Losonsky JM, et al. Aspirin and prednisolone modification of post-adulticide pulmonary arterial disease in heartworm infection: Arteriographic study. Am J Vet Res 44:821, 1983
60. Rawlings CA, Keith JC, Lewis RE, et al. Aspirin and prednisolone modification of radiographic changes caused by adulticide treatment in dogs with heartworm infection. J Am Vet Med Assoc 182:131, 1983
61. Losonsky JM, Thrall D, Lewis RE. Thoracic radiographic abnormalities in 200 dogs with spontaneous heartworm infections. Vet Radiol 24:120, 1983
61a. Dunavent B, Keister DM, Tanner P, et al. Correlation between heartworm disease classification, serum antigen concentration, and associated clinical pathology parameters; Abstract. Program of the 8th Triennial State of the Heartworm Symposium, 1995, p 48
62. Atwell RB, Searle AC. Adulticide efficacy and safety of RM 340 in a field trial. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Charleston, SC, American Heartworm Society, 1989, p 143
63. Dzimianski MT, McTier TL, McCall JW. Assessment of filaricidal activity of a new filaricide (RM 340) against immature and adult heartworms using experimental canine nodules. *In* Otto GF (ed): Proceedings, Heartworm Symposium, Charleston, SC, American Heartworm Society, 1989, p 147
64. Hoskins JD, Hagstad HV, Hribernick TN. Effects of thiacetarsamide sodium in Louisiana dogs with naturally occurring canine heartworm disease. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Orlando, FL, Veterinary Medical Publishing Company, 1983, p 134
65. Sundlof SF, Courtney CH, Bell JV, et al. Pharmacokinetics of thiacetarsamide in relationship to therapeutic efficacy. *In* Otto GF (ed): Proceedings, Heartworm Symposium. New Orleans, American Heartworm Society, 1986, p 65
66. Keister DM, Dzimianski MT, McTier TL, et al. Dose selection and confirmation of RM 340, a new filaricide for the treatment of dogs with immature and mature *Dirofilaria immitis*. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 225
67. Miller MW, Keister DM, Tanner PA, et al. Clinical efficacy and safety trial of melarsomine dihydrochloride

(RM 340) and thiacetarsemide in dogs with moderate (Class 2) heartworm disease. Program of the 8th Triennial State of the Heartworm Symposium, 1995, p 49
68. Rawlings CA, Raynaud JP, Lewis RE, et al. Pulmonary thromboembolism and hypertension after thiacetarsamide vs. melarsomine dihydrocholoride treatment of *Dirofilaria immitis* infection in dogs. Am J Vet Res 54:920, 1993
69. McCall JW, McTier MT, Dzimianski JP, et al. Clinical prophylactic activity of melarsomine dihydrochloride (RM 340) against *Dirofilaria immitis* in heartworm-naive beagles exposed to natural infection in three southeastern states. Vet Parasitol 52:194, 1994
70. King R. Clinical implications of a highly effective adulticide. Proceedings, The North American Veterinary Conference. Vol 8. Orlando, FL, 1994, p 458
71. Tanner PA, Winograd H, Keister DM. Clinical field trial for the treatment of mature and immature *Dirofilaria immitis* infestation in dogs with severe heartworm disease. Proceedings, 38th Annual Meeting, American Association of Veterinary Parasitologists. Minneapolis, July 17–20, 1993
72. Holmes RA, Wilson RA, McCall JW. Thiacetarsamide in dogs. Disposition, kinetics, and correlations with selected indocyanine green kinetic values. Am J Vet Res 47:1338, 1986
73. Holmes RA. Thiacetarsamide Na: Pharmacokinetics and the effects of decreased liver function on efficacy against *Dirofilaria immitis* in dogs. *In* Otto GF (ed): Proceedings, Heartworm Symposium. New Orleans, American Heartworm Society, 1986, p 57
74. Rawlings CA, Keith JC, McCall JW. Thiacetarsamide efficacy. One more study using a different research model. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Orlando, FL, Veterinary Medical Publishing Company, 1983, p 141
75. McCall JW, Lewis RE, Rawlings CA, et al. Reevaluation of thiacetarsamide as an adulticidal agent against *Dirofilaria immitis* in dogs. *In* Otto GF (ed): Proceedings, Heartworm Symposium, 1980. Edwardsville, KS, Veterinary Medicine Publishing Company, 1981, p 141
76. Blair LS, Malatesta PF, Gerckens LS. Efficacy of thiacetarsamide in experimentally infected dogs at 2, 4, 6, 12, or 24 months post-infection with *Dirofilaria immitis. In* Otto GF (ed): Proceedings, Heartworm Symposium. Orlando, FL, Veterinary Medicine Publishing Company, 1983, p 130
77. Courtney CH, Sunlof SF, Jackson RF. New dose schedule for the treatment of canine dirofilariasis with thiacetarsamide. *In* Otto GF (ed): Proceedings, Heartworm Symposium. New Orleans, American Heartworm Society, 1986, p 49
78. Vezzoni A, Genchi C. Reduction of post-adulticide thromboembolism complications with low dose heparin therapy. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Charleston, SC, American Heartworm Society, 1989, p 73
79. Rawlings CA, Keith JC, Schaub RG. Effect of acetylsalicylic acid on pulmonary arteriosclerosis induced by a one-year *Dirofilaria immitis* infection. Arteriosclerosis 5:355, 1985
80. Rawlings CA, Keith JC, Schaub RC. Aspirin and corticosteroids in the treatment of heartworm disease. *In* Otto GF (ed): Proceedings, Heartworm Symposium. New Orleans, American Heartworm Society, 1986, p 139
81. Atwell RB, Sutton RH, Carlisle CH. Reduction of pulmonary thromboembolic disease *(D. immitis)* in the dog associated with aspirin therapy. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Orlando, FL, Veterinary Medicine Publishing Company, 1983, p 115
82. Keith JR, Rawlings CA, Schaub RG. Effect of aspirin therapy on canine pulmonary artery disease caused by *Dirofilaria immitis. In* Otto GF (ed): Proceedings, Heartworm Symposium. Orlando, FL, Veterinary Medicine Publishing Company, 1983, p 519
83. Keith JC, Rawlings CA, Schaub RG. Pulmonary thromboembolism during therapy of dirofilariasis with thiacetarsamide modified with aspirin or prednisolone. Am J Vet Res 44:1278, 1983
84. Schaub RG, Keith JC, Rawlings CA. Effect of long-term aspirin treatment on platelet adhesion to chronically damaged canine pulmonary arteries. Thromb Haemost 46:680, 1981
85. Schaub RG, Keith JC, Rawlings CA. The effect of acetylsalicylic acid on vascular damage and myointimal proliferation in canine pulmonary arteries subjected to chronic injury by *Dirofilaria immitis* infection. Am J Vet Res 44:449, 1983
86. Rawlings CA, Keith JC, Losonsky JM, et al. An aspirin-prednisolone combination to modify postadulticide lung disease in heartworm-infected dogs. Am J Vet Res 45:2371, 1984
87. Neilson JA, Atwell RB. Experimental therapy choices for thromboembolism in heartworm disease. *In* Otto GF (ed): Proceedings Heartworm Symposium. Charleston, SC, American Heartworm Society, 1989, p 67
88. Leuthy MW, Sisson DD, Kneller SK, et al. Angiographic assessment of aspirin and heparin therapy for the prevention of pulmonary thromboembolism following adulticide therapy. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Charleston, SC, American Heartworm Society, 1989, p 53
89. Atwell RB, Van Kan DM, Cottis LE, et al. The use of antigen test for diagnosis as an indicator of filarial numbers, and for assessing filarial mortality following thiacetarsamide therapy. *In* Otto GF (ed): Proceedings, Heartworm Symposium. New Orleans, American Heartworm Society, 1986, p 71
90. Recommended procedures for the diagnosis and management of heartworm *(Dirofilaria immitis)* infection. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Charleston, SC, American Heartworm Society, 1989, p 230
91. Recommended procedures for the diagnosis and management of heartworm *(Dirofilaria immitis)* infection. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 289
92. Calvert CA, Losonsky JM. Occult heartworm disease-associated allergic pneumonitis. J Am Vet Med Assoc 186:1097, 1985
93. Wong MM, Guest MF. Filarial antibodies and eosinophilia in human subjects in an endemic area. Trans R Soc Trop Med Hyg 63:796, 1969
94. Weingarten RJ. Tropical eosinophilia. Lancet 1:103, 1943
95. Van der Sar S, Hartz H. The syndrome, tropical eosinophilia and microfilaria. Am J Trop Med Hyg 25:83, 1945
96. Liebow AA, Hannum CA. Eosinophilia, ancylostomiasis, and strongyloidosis in the South Pacific area. Yale J Biol Med 18:381, 1976
97. Raich RA, Gleason DF. Pulmonary symptoms and eosinophilia due to filariasis. Tubercle 50:462, 1959
98. Donohugh DL. Tropical eosinophilia. An etiologic inquiry. N Engl J Med 269:1357, 1963
99. Confer AW, Qualls CW, MacWilliams RS, et al. Four cases of pulmonary nodular eosinophilic granulomatosis in dogs. Cornell Vet 73:41, 1983

100. Calvert CA, Rawlings CA. Pulmonary manifestations of heartworm disease. Vet Clin North Am 15:991, 1985
101. Calvert CA, Mahaffey MD, Lappin MR, et al. Pulmonary and disseminated eosinophilic granulomatosis in dogs. J Am Anim Hosp Assoc 24:311, 1988
102. Berry CR, Moore PF, Thomas WP, et al. Pulmonary lymphomatoid granulomatosis in seven dogs (1976–1987). J Vet Intern Med 4:157, 1990
103. Jackson RF, Seymour WG, Growney PJ, et al. Surgical treatment of the caval syndrome of canine heartworm disease. J Am Vet Med Assoc 171:1065, 1977
104. Osburn PN, Jackson RF, Seymour G, et al. Electrocardiographic and phonocardiographic alterations in canine heartworm disease. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Atlanta, Veterinary Medicine Publishing Company, 1977, p 67
105. Ishihara K, Kitagawa H, Ojima M, et al. Clinicopathological studies in canine dirofilaria hemoglobinuria. J Vet Sci 40:525, 1978
106. Atwell RB, Farmer TS. Clinical pathology of the caval syndrome in canine dirofilariasis in Northern Australia. J Small Anim Pract 23:675, 1982
107. Atkins CE, Keene BW, McGuirk SM. Investigation of caval syndrome in dogs experimentally infected with *Dirofilaria immitis.* J Vet Intern Med 2:36, 1988
108. Atkins CE, Keene BW, McGuirk SM. Pathophysiology of cardiac dysfunction in an experimental model of heartworm caval syndrome in the dog. Am J Vet Res 49:403, 1988
109. Atkins CE. Caval syndrome in the dog. Semin Vet Med Surg 2:64, 1987
110. Atkins CE. Pathophysiology of heartworm caval syndrome: Recent advances. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Charleston, SC, American Heartworm Society, 1989, p 27
111. Rawlings CA, Tackett RL. Postadulticide pulmonary hypertension of canine heartworm disease: Successful treatment with oxygen and failure of antihistamines. Am J Vet Res 51:1565, 1990
112. Jackson RF. Ivermectin again. Am Heartworm Soc Bull 10:9, 1984
113. Jackson RF, Seymour WG, Beckett RS. Lower dose of ivermectin as a microfilaricide. *In* Otto GF (ed): Proceedings, Heartworm Symposium. New Orleans, American Heartworm Society, 1986, p 15
114. Jackson RF, Seymour G, Beckett RS. Routine use of 0.05 mg/kg of ivermectin as a microfilaricide. *In* Otto GF (ed): Proceedings, Heartworm Symposium, New Orleans, American Heartworm Society, 1986, p 37
115. Neer TM, Hoskins JD. Clinical experience with ivermectin used as a microfilaricide and for prophylaxis in the dog. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Charleston, SC, American Heartworm Society, 1989, p 95
116. Paul AJ, Tranquilli WJ, Seward RH, et al. Clinical observations in collies given ivermectin orally. Am J Vet Res 48:684, 1987
117. Pulliam JD, Seward RL, Henry RT. Investigating ivermectin toxicity in collies. Vet Med 80; 39, 1985
118. Blagburn BL, Hendrix CM, Lindsay DS, et al. Post-adulticide, milbemycin oxime microfilaricidal activity in dogs naturally infected with *Dirofilaria immitis. In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 159
119. McTier TL, McCall JW, Dzimianski MT, et al. Epidemiology of heartworm infection studied by using naturally exposed "tracer" beagles in three southeastern states. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 47
120. Fortin JF. Development of *Dirofilaria immitis* in *Aedes triseriatus* and *Aedes vexans* at different temperatures. Master's thesis. University of Guelph, Ontario, Canada, 1979
121. Palumbo NE, Perri SF, Desovitz SR, et al. Preliminary observations on adverse reactions to diethylcarbamazine (DEC) in dogs infected with *Dirofilaria immitis. In* Otto GF (ed): Proceedings, Heartworm Symposium. Atlanta, Veterinary Medicine Publishing Company, 1977, p 97
122. Powers DG, Parbuoni EL, Furrow RD. *Dirofilaria immitis.* I. Adverse reactions associated with diethylcarbamazine therapy in microfilaremic dogs. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Atlanta, Veterinary Medicine Publishing Company, 1977, p 108
123. Rawlings CA, Greene CE, Dawe DL, et al. Diethylcarbamazine; Adverse reaction and relationship to microfilaremia. *In* Otto GF (ed): Proceedings, Heartworm Symposium. New Orleans, American Heartworm Society, 1986, p 143
124. Atwell RB, Boreham PFL. Studies on the adverse reactions following diethylcarbamazine to microfilaria-positive *(D. immitis)* dogs. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Orlando, FL, Veterinary Medicine Publishing Company, 1983, p 83
125. McCall JW, Evans TL, Lidemann BA, et al. Chemoprophylaxis of experimentally induced heartworm and hookworm infections in dogs. Mod Vet Pract July/Aug 1987, p 417
126. Lok JB, Knight DH, Ramadan E-S. Effects of ivermectin on embryogenesis in *Dirofilaria immitis*: Age, structure and spatial distribution of intrauterine forms as a function of dosage and time post treatment. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Charleston, SC, American Heartworm Society, 1989, p 85
127. Lok JB, Knight DH, LaPaugh DA, et al. Kinetics of *Dirofilaria immitis* microfilaremia suppression in dogs during and after a prophylactic regimen of milbemycin oxime. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 143
128. Bowman DD, Johnson RB, Ulrich ME, et al. Effects of long-term administration of ivermectin and milbemycin oxime on circulating microfilariae and parasite antigenemia in dogs with patent heartworm infection. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 151
129. Dzimianski MT, McCall JW, Roberson EL, et al. Prevention of heartworm infection and clearance of ascarid and hookworm infections in dogs using a chewable formulation of ivermectin plus pyrantel pamoate. *In* Soll MD (ed): Proceedings, Heartworm Symposium, Austin, TX, American Heartworm Society, 1992, p 201
130. McCall JW, Lindemann BA, Porter CA. Prophylactic activity of ivermectin against experimentally induced *Dirofilaria immitis* in dogs. *In* Otto GF (ed): Proceedings, Heartworm Symposium, 1980. Edwardsville, KS, Veterinary Medicine Publishing Company, 1981, p 126
130a. McCall JW, McTier T, Supakorndej N, et al. Clinical prophylactic activity of macrolides on young adult heartworms; Abstract. Program of the 8th Triennial State of the Heartworm Symposium, 1995, p 45
131. Bater AK. Efficacy of oral milbemycin against naturally acquired heartworm infections in dogs. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Charleston, SC, American Heartworm Society, 1989, p 107
132. Blagburn BL, Hendrix CM, Linsday DS, et al. Milbemycin: Efficacy and toxicity in beagle and collie dogs.

In Otto GF (ed): Proceedings, Heartworm Symposium. Charleston, SC, American Heartworm Society, 1989, p 109

133. Bradley RE. Dose titration and efficacy of milbemycin oxime for prophylaxis against *Dirofilaria immitis* infection in dogs. *In* Otto GF (ed): Proceedings, Heartworm Symposium. New Orleans, American Heartworm Society, 1989, p 115
134. McTier TL, McCall JW, Dzimianski MT, et al. Prevention of experimental heartworm infection in dogs with single, oral doses of moxidectin. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 165
135. Grieve RB, Frank GR, Stewart VA. Effect of dosage and timing on heartworm chemoprophylaxis with milbemycin. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 121
136. McCall JW, McTier TL, Holmes RA, et al. Prevention of naturally acquired heartworm infection in heartworm-naive beagles by oral administration of moxidectin at an interval of either one or two months. *In* Soll MD (ed): Proceedings, Heartworm Symposium, Austin, TX, American Heartworm Society, 1992, p 169
137. King RL, Courtney CH, Aguilar R. Heartworm prophylaxis with moxidectin: Field trials from a hyperendemic area. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 179
138. Paul AJ, Tranquilli WJ, Todd KS, et al. Evaluation of safety of moxidectin in collies. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin TX, American Heartworm Society, 1992, p 189
139. Hendrix CM, Blagburn BL, Bowles JV, et al. Safety of moxidectin in dogs infected with microfilariae and adults of *D. immitis*. *In* Soll MD (ed): Proceedings, Heartworm Symposium. Austin, TX, American Heartworm Society, 1992, p 183

31 Feline Heartworm Disease

RAY DILLON

Dirofilaria immitis infection has been reported worldwide in cats and is consistently diagnosed in heartworm-endemic areas.[1-14] The increased awareness of the disease has made antemortem diagnosis more common.[15-19] The frequency of feline heartworm infection correlates with that of dogs in the same geographic area, but at a lower incidence.

HEARTWORM INFECTION

ADULT HEARTWORMS

Heartworm disease is more difficult to produce experimentally in cats than in dogs.[12, 20-25, 26] Moreover, the percentage of infective larvae (L_3) developing into adult worms is significantly less in cats (1 to 25%) than in dogs (40 to 90%). Cats are most at risk in heavily endemic areas where repeated bites by infected mosquitos are common. Experimentally, when adequate infective larvae are used, the percentage of infective larvae developing to adult *D. immitis* is low, but the percentage of cats from which adult worms are recovered is high (66 to 90%). It appears that infective larvae in the cat are poorly oriented, and adult worms are more likely to develop at ectopic sites (brain, eye, subcutaneous tissue) than in the dog. After experimental injections of L_3 in the cat, abnormal migration patterns result in death of migrating larvae, subcutaneous nodules, and granuloma formation.[21, 22]

Normally the adult worm burden is less in the cat (range, usually 1 to 9 worms) compared with the dog. Although adult worms reach significant size in the cat (female > 21 cm, male > 12 cm), their development seems to be slower than in the dog.[22, 26]

Adult heartworms in the cat have a relatively short life span (probably < 2 years) compared to the dog (approximately 5 years).[22, 26, 27] The shortened longevity of adult worms contributes to an underestimation of the prevalence of heartworm disease in the cat based on routine necropsy examination of the general population. A gradual decrease in the number of immature worms found in the heart has been noted when cats are chronologically studied.[22, 26] Compared with dogs, the cat is a relatively more resistant, but still susceptible, host for *D. immitis.*

INFECTIVE LARVAE

Once infected by adult heartworms via infective (L_3) larvae or by experimental transplantation, the cat's natural resistance results in a shortened

period of patency, lower heartworm numbers, or lack of microfilaremia.[3, 21, 22] The average time for infective larvae to develop into circulating microfilariae in experimental feline infections is about 8 months. The comparable period in the dog is 5 to 6.5 months.

The cat is not an important host for *D. immitis.* Infective larvae developed in about 1 percent of *Anopheles* sp. and *Aedes* sp. mosquitos that fed on cats with patent infections.[22] For a cat to become infected, a mosquito must bite an animal with a patent infection (usually a dog) and then, after proper climate conditions, bite a cat. Some mosquito species feed on both dogs and cats whereas others prefer one or the other. The propensity of some mosquitos to prefer felines may account for regionally high incidences of feline heartworm disease (up to 18%) reported in some areas.

MICROFILARIAE

Microfilaremia is uncommon (< 20% of spontaneous clinical cases), inconsistent, and, in cats, transient. Very low numbers are usually produced (e.g., six experimental cats had > 2 microfilariae/ml blood). Therefore, concentration tests are recommended for diagnosis, and a negative test does not rule out heartworm disease. For this reason, some have advocated that greater volumes of blood be used when performing a microfilaria concentration test.

PATHOPHYSIOLOGY

Pulmonary pathology in feline heartworm disease is similar to that described in the dog.[2, 20, 22] Muscular hypertrophy, villous endarteritis, and adventitial cellular infiltrates are common and typically more severe in the caudal pulmonary arteries. Pulmonary fibrosis and smooth muscle hyperplasia can occur. The smaller pulmonary arteries develop severe muscular hypertrophy in infected cats, however, and pulmonary arteries may become radiographically enlarged within 1 week of experimental heartworm transplantation.[2, 3] Embolization of pulmonary arteries is a major factor contributing to initiation of clinical signs. However, severe cor pulmonale is uncommon in affected cats, and associated clinical changes, including electrocardiographic right axis deviation, radiographic right-sided heart enlargement, and right-sided heart failure are infrequent.[3]

Obstruction of blood flow, especially to the caudal pulmonary arteries, may cause acute clinical signs. However, the majority of clinical signs are associated with acute lung injury. Affected lung lobes become hemorrhagic, with areas of necrosis and insult. If the cat survives the initial pulmonary embolism, recanalization around the obstruction occurs rapidly, and the lung markedly improves within days. The result of the acute lung injury is Type II alveolar cell hypertrophy.

Postcaval syndrome with ascites and right-sided heart failure occurs rarely and accompanies very high worm burdens. Hemoglobinuria has not been a consistent finding in these infected cats. Clinical signs appear to be associated with poor venous return and tricuspid insufficiency rather than due to severe hypertension.

CLINICAL MANIFESTATIONS

EPIDEMIOLOGY

There is no age predilection in feline heartworm disease. Reported ages incorporate a wide range (1 to 17 yrs).[3, 13, 15, 16] Indoor and outdoor cats may become infected, but outdoor cats seem to be more prone to infection.[16a] A higher incidence in males compared to females has been demonstrated experimentally. In naturally infected cats, males generally have an increased risk of exposure. Feline leukemia virus infection is not a predisposing factor, and heartworms are not a common finding at necropsy in cats with FeLV.[3] The prevalence of heartworm infection in pet cats with cardiorespiratory abnormalities in the southeastern and southwestern United States was reported to be 9 percent.[16a]

HISTORY

Clinical features are generally referable to the cardiopulmonary, gastrointestinal, or nervous systems or are nonspecific. Coughing, dyspnea, vomiting, lethargy, anorexia, and weight loss are the most common historical complaints.[2a, 3, 16a] In chronic infections, vomiting or respiratory signs predominate, although usually not together. Anorexia and lethargy can be the only presenting signs in some cats.

When vomiting occurs it tends to be sporadic and unrelated to eating. The cause is unknown; however, release of inflammatory lung mediators with resultant chemoreceptor trigger zone stimulation and emesis has been postulated. The vomitus generally contains food or foam but is rarely bile stained.

Coughing can be severe and paroxysmal, with intervening periods (days to weeks) of normality. Dyspnea may be sudden and may represent acute disease associated with worm death. Corticosteroids may temporarily ameliorate respiratory signs. Hemoptysis is occasionally noted.

Occasionally, aberrant heartworm migration may cause abnormalities attributable to local pathology.

TABLE 31-1
Clinical Signs Associated with Feline Heartworm Disease

Acute Signs	Chronic Signs
Sudden death*	PIE† syndrome
Respiratory	Coughing
Pulmonary embolism	Dyspnea
Collapse; shock	Cardiopulmonary
Hemoptysis	Lethargy
Dyspnea; cough	Weakness
Pneumonitis	Right-sided CHF‡
Dyspnea; cough	Anorexia
Neurologic	Gastrointestinal
Blindness	Vomiting
Seizures	
Ataxia	
Coma	
Circling	
Syncope	
Vomiting	

*From severe pulmonary thromboembolism or heartworm occlusion of main pulmonary artery.
†Pulmonary infiltrates of eosinophilia.
‡Congestive heart failure.
Modified from Calvert C. Feline heartworm disease. *In* Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 555.

Neurologic signs are uncommon but have been reported with[3, 5, 28, 29] and without worms physically present within the central nervous system.

CLINICAL FEATURES

Infected cats may die acutely, exhibit chronic signs, or be asymptomatic (Table 31-1). In the acute cases, death may be so rapid as to preclude diagnosis or treatment. Acute collapse may occur with or without previous clinical signs. Sudden death has been attributed to circulatory collapse and respiratory failure due to acute pulmonary arterial infarction and lung injury.[13, 30, 31] As few as one worm has been found at necropsy accompanied by severe pulmonary congestion, infarction, and edema. Worms are not always found embolizing the main pulmonary arteries.

When clinical signs occur, they are most commonly associated with immature heartworms arriving in the lungs or death of adult heartworms. The initial arrival of L_5 larval stages in the distal pulmonary arteries induces diffuse pulmonary infiltrates and often eosinophilic pneumonitis. On occasion, occlusion of a pulmonary artery (right caudal being the most common) by a dead or dying adult worm is associated with life-threatening, acute dyspnea.[2] Predictably, clinical signs associated with early infections occur in the late fall and early winter months, 4 to 7 months after exposure. Antigen testing at this time is usually negative because the worms are immature.

After an initial host response, clinical signs may abate for a period of time. However, the death of the adult heartworms usually heralds the onset of severe signs.

PHYSICAL EXAMINATION FINDINGS

There are no abnormal findings in many infected cats. In others, signs are nonspecific or referable to the cardiopulmonary or nervous system. A systolic murmur may be heard over the tricuspid valve area and, occasionally, a gallop rhythm can be present. Harsh lung sounds are the most frequent abnormal auscultatory finding and can be present even in cats that do not exhibit respiratory signs. Ascites, exercise intolerance, and right-sided heart failure are rare. There does not seem to be a correlation between the clinical signs, physical examination abnormalities, and radiographic changes.

DIAGNOSTIC TESTING

When clinical signs consistent with heartworm infection are detected, a data base should be generated. A number of tests may be useful when evaluating a cat for heartworm disease (Table 31-2).

CLINICAL PATHOLOGY

Mild, nonregenerative anemia or peripheral eosinophilia is present in about one third of infected cats. The latter depends on the stage of infective larvae, occurring 4 to 7 months postinfection.[21, 22] The absence of eosinophilia does not exclude a diagnosis of feline heartworms.[2, 3] Bronchial alveolar lavage fluid may contain eosinophils in the absence of peripheral eosinophilia. As in the dog, basophilia is highly suggestive of heartworm disease but is a rare finding. Serum biochemistries and urinalysis are usually normal. Hyperglobulinemia occurs in some cats[15] but is not consistent or predictable.[3, 27] Normal serum globulins and protein electrophoresis can be recorded in cats that

TABLE 31-2
Diagnostic Testing for Suspected Feline Dirofilariasis

Thoracic radiographs
Serology to detect feline antibody against adult antigen
Serology to detect adult antigen
Nonselective angiocardiogram
Knott's test
Echocardiogram
CBC/differential
Tracheal wash or bronchoalveolar lavage
Electrocardiogram
Fecal examination

test positive for heartworm with a Knott's test, antibody test, or antigen test.

MICROFILARIAE CONCENTRATION TESTS

Since microfilaremia, when present, is characterized by short duration and low numbers, most cats with heartworms are not microfilaremic when evaluated. Therefore, a positive blood test for microfilariae is unlikely but diagnostic when present. Diagnostic accuracy is increased when large quantities of blood (5 ml) are evaluated by concentration tests such as Knott's tests or filter techniques. Even with repetitive testing, over 80 percent of feline heartworm disease is amicrofilaremic.

SEROLOGY

Three types of serologic tests have been used to detect feline heartworm disease: (1) an immunofluorescent antibody (IFA) test that detects antibodies directed against microfilarial antigens; (2) an enzyme-linked immunosorbent assay (ELISA) that detects antibodies against adult worm antigens; and (3) serologic tests (ELISA or colloid gold) that detect adult heartworm antigen. Given the high incidence of occult disease in the cat, serologic tests are usually valuable.[2a, 16a]

IFA TEST. The IFA test detects antibodies to microfilarial cuticular antigen. It is diagnostic about one third of the time. However, immature or sterile worms or unisex worms in cats or the absence of a host response to antigen does not produce a diagnostic titer.[16] Use of the somatic IFA (detecting antibodies to microfilarial somatic antigen) is nonspecific.[26] These assays have been helpful in researching the biology of the parasite-host interaction but have limited clinical application.

ELISA TESTS. The ELISA test denotes a method of analysis. Antigen preparation, antibody sources, and techniques can vary among diagnostic laboratories. Therefore, results may vary among assays. An ELISA to detect feline antibodies in the serum to L_4 *D. immitis* antigen has shown some promise, but false-positives related to cross-reactivity have been a concern.[26, 32] The use of the ELISA adapted from canines[32, 33] to confirm feline infections has been helpful, and false-positives from cross-reactivity have not been observed. However, methods used in canine testing to measure dog antibody to *D. immitis* cannot be used on cat sera.[27]

Cats that have eliminated the adult parasite naturally or after adulticidal therapy develop a negative ELISA titer when the host antibody gradually decreases to negative concentrations (i.e., 4 to 6 months). Because the antibody being detected is produced by the cat in response to the early migration of the L_3 or L_4, positive titers are detected about 2 to 3 months after exposure. This is important in cats in which immature worms cause clinical signs and in which the antigen test will be negative. However, with the use of macrolides as a preventive medication, larvae can initiate a positive antibody response and then be killed by the macrolide. This produces an antibody-positive response although, in reality, the cat does not have adult heartworms. A positive antibody result indicates that a cat has been infected with L_3, the L_3 has molted into L_4, and the parasite has lived at least 2 to 3 months. However, an adult infection may or may not have developed.

HEARTWORM ANTIGEN. Detection of heartworm antigen in blood or serum has been used successfully in dogs. These tests have been positive in cats within days of transplantation of mature adult worms from dogs into cats. However, since the antigen being detected seems to be derived primarily from the adult female heartworm reproductive tract, inadequate antigen may be present for detection with immature infections, a low worm burden, a male infection, or with sexually immature worms. Cats given large numbers of infective larvae experimentally may develop positive antigen tests 8 months later. However, cats with active heartworm disease and high antibody titers can test negative for antigen. Thus, because clinical signs are usually associated with immature worms, and since adult heartworms mature slowly in low numbers, it would be prudent to consider that a positive antigen test is diagnostic, but that a negative test does not rule out heartworms. With elimination of the adult parasite, the antigen test becomes negative.

CYTOLOGY

Eosinophils are commonly identified by cytology from the tracheal wash or bronchoalveolar lavage of cats with heartworm disease, as well as with other respiratory disorders. Cytologic eosinophilia seems to be prevalent 4 to 7 months after experimental L_3 infection but may not be present later in the infection, even when adult worms are present. Chronic inflammation may be present after the eosinophilic reaction resolves.

ELECTROCARDIOGRAPHY

Although electrocardiographic evidence of right ventricular enlargement is occasionally indicated from unipolar chest leads,[15, 34] detection of a right axis deviation greater than 120 degrees is rarely present on a standard 6-lead ECG.[3] Ectopic ventricular beats and

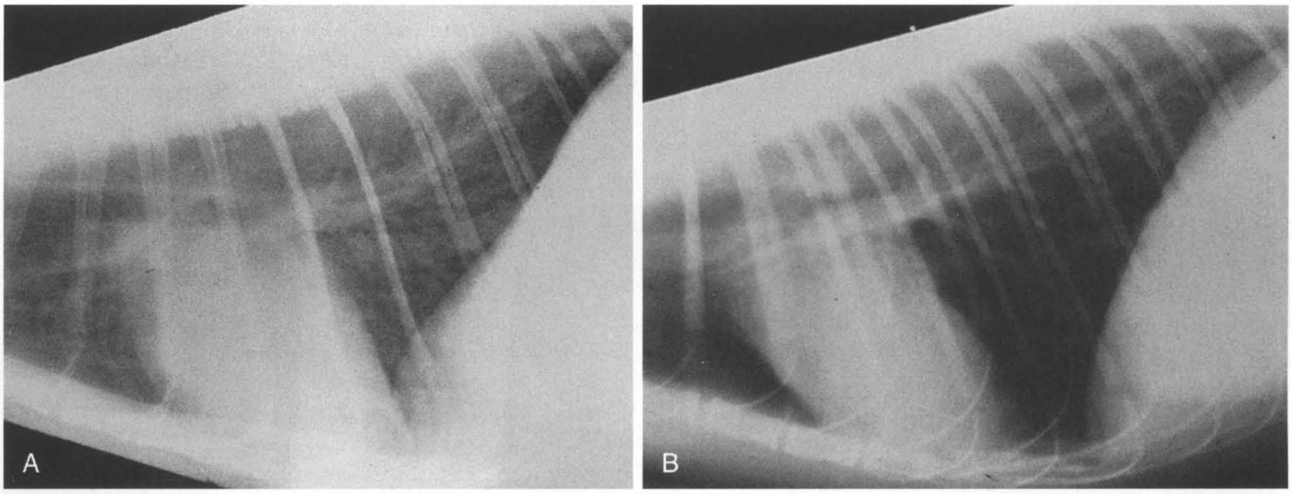


FIGURE 31–1

Right lateral thoracic radiographs of a coughing, dyspneic cat with dirofilariasis and allergic pneumonitis before (A) and 3 days after (B) corticosteroid therapy (prednisolone, 5 mg bid). (A) There is a generalized pulmonary interstitial pattern. Moderate right-sided heart enlargement is present. Lobar pulmonary arteries were slightly enlarged on the ventrodorsal but not lateral view. This cat had peripheral eosinophilia, hyperglobulinemia, and a positive indirect fluorescent antibody test for microfilarial cuticular antigen. (B) Postcorticosteroid therapy radiograph shows dramatic clearing of the pulmonary interstitial pattern and slight reduction in right-sided cardiac enlargement. Clinically, coughing was reduced. (From Calvert CA. Feline heartworm disease. *In* Fox PR (ed): Canine and Feline Cardiology. 1st ed. New York, Churchill Livingstone, 1988, p 551.)

other arrhythmias are rarely present after adulticide therapy in asymptomatic cats.

RADIOGRAPHY

Radiology is one of the best screening tests for feline heartworm disease. Pulmonary parenchymal changes are nonspecific and can change rapidly in infected cats (Fig. 31–1). They include interstitial infiltrates, diffuse or coalescing infiltrates, perivascular densities, and lung atelectasis[4, 17, 35, 36] (Fig. 31–2).

The most distinctive radiographic sign of feline heartworm disease is enlarged pulmonary arteries with ill-defined margins (Figs. 31–3, 31–4). This is most prominent in the caudal lung lobes on the ventrodorsal view. Blunting and tortuosity of the pulmonary arteries are occasionally seen, but not as commonly as in the dog. An enlarged main pulmonary arterial segment extending beyond the cardiac border on the ventrodorsal or dorsoventral view is not a classic feature of feline heartworms. A nonselective angiocardiogram may demonstrate enlarged pulmonary arteries and pulmonary emboli[4, 33, 35] (Fig. 31–4) and is an accurate method for confirming a diagnosis of heartworms.

ECHOCARDIOGRAPHY

When adult heartworms are present in the right ventricle or main pulmonary artery, they are readily detectible by echocardiography[36a] (Fig. 31–5). Nonspecific changes may be noted, including right ventricular enlargement and hypertrophy, and increased main pulmonary artery.

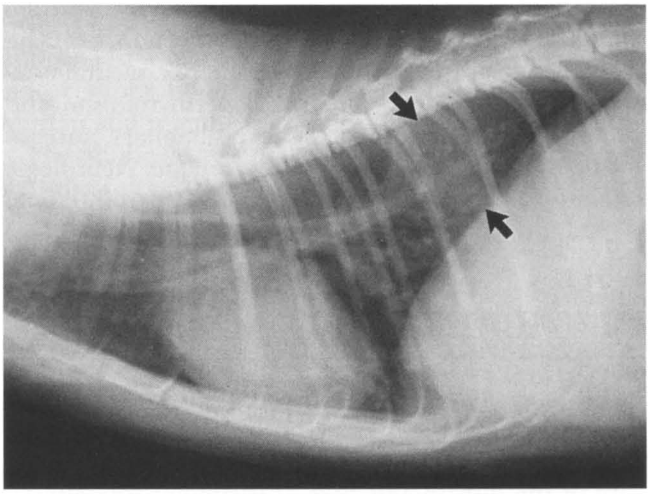


FIGURE 31–2

Right lateral thoracic radiograph from a cat with dyspnea and coughing. There is a generalized pulmonary interstitial pattern infiltrate. Notice the patch of dense, alveolar pattern infiltrate *(arrows)* in the dorsocaudal lung region. A smaller patch is present just ventral to the caudal vena cava. Right-sided cardiomegaly is evidenced by the increased sternal contact and pronounced cranial waist. The ventrodorsal radiograph (not pictured) showed caudal lung lobe alveolar pattern infiltrates and right-sided heart enlargement. These findings were consistent with dirofilariasis and pulmonary infarcts. (From Calvert CA. Feline heartworm disease. *In* Fox PR (ed): Canine and Feline Cardiology. 1st ed. New York, Churchill Livingstone, 1988, p 551.)

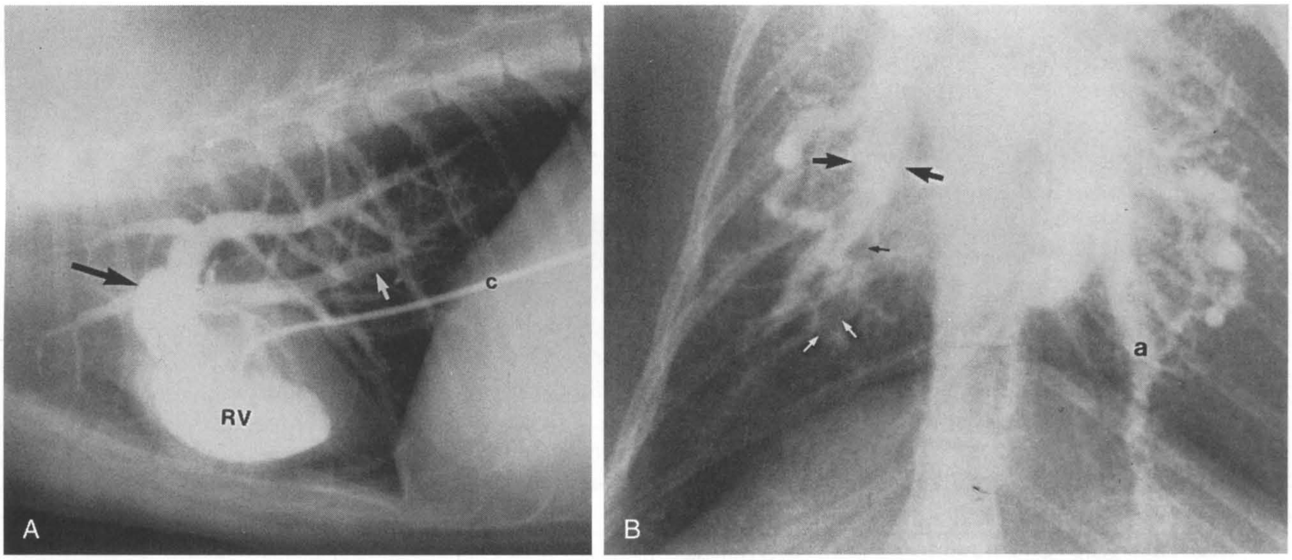


FIGURE 31–3

Selective right ventricular angiocardiogram of a cat infected with heartworms. (A) Right lateral view. The main pulmonary artery is enlarged *(black arrow)*, and caudal lobar artery enlargement is evident *(white arrow)*. In addition, the right ventricle *(RV)* is enlarged, as evidenced by increased sternal contact and cardiac apex tipping. *C*, catheter. (B) Ventrodorsal view. Compared with the left caudal lobar artery, the right lobar artery is enlarged *(large arrows)* and obstructed *(small arrows)*. Lobar pulmonary arteries are tortuous. *a*, left caudal lobar artery. (From Calvert CA. Feline heartworm disease. *In* Fox PR (ed): Canine and Feline Cardiology. 1st ed. New York, Churchill Livingstone, 1988, p 551.)

DIFFERENTIAL DIAGNOSIS

In the cat with respiratory signs, heartworm disease must be differentiated from *Aelurostrongylus abstrusus* (lungworm) or *Paragonimus kellicotti* infection, bronchitis or asthma, cardiomyopathy, pyothorax, pleural effusions, pneumothorax, anemia, hyperthyroidism, and other systemic disorders. The pulmonary arterial changes of heartworm disease are unique. Neurologic conditions and disorders involving the gastrointestinal system must sometimes be considered.

CLINICAL MANAGEMENT

The decision whether or not to treat feline heartworms is often complicated by the unpredictable nature of the disease and risks of treatment side effects. The latter seem to more severe than in the dog.[2] In symptomatic cats, for example, clinical signs may be chronic and intermittent, leading one into believing that the disease is not severe. However, spontaneous acute complications or death can occur in a small percentage of untreated animals. In contrast, this risk appears to be small in the asymptomatic cat compared with the complications of adulticidal therapy. Adult heartworms have a shorter longevity in the cat compared with the dog, and spontaneous recovery is always possible.[27] However, the natural death of adult worms can be associated with severe respiratory signs. Some cats managed conservatively by intermittent corticosteroid therapy will develop peracute signs and die from heartworm disease. In the cat with recurrent life-threatening dyspnea or with severe clinical signs, adulticidal therapy should be considered. The poten-

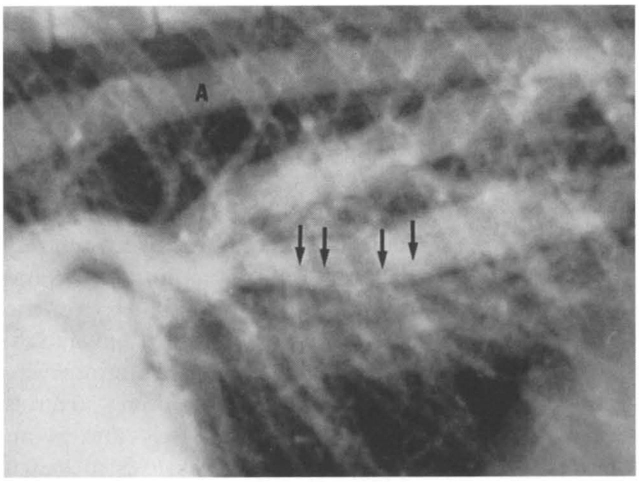


FIGURE 31–4

Nonselective angiocardiogram (right lateral view) of a vomiting cat with heartworm infection. Notice the caudal lobar pulmonary artery enlargement, tortuosity, and pruning. There are linear filling defects *(arrows)* in the pulmonary arteries caused by adult heartworms. *A*, descending aorta. (From Calvert CA. Feline heartworm disease. *In* Fox PR (ed): Canine and Feline Cardiology. 1st ed. New York, Churchill Livingstone, 1988, p 551.)

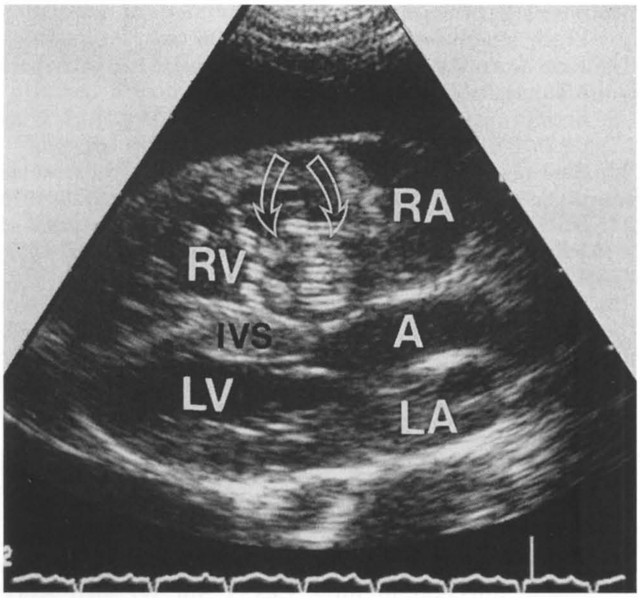


FIGURE 31-5

Two-dimensional echocardiogram (right parasternal long-axis view) of a cat with heartworm infection and right-sided congestive heart failure. Both the right atrium *(RA)* and right ventricle *(RV)* are enlarged. Notice the large mass of heartworms *(arrows)*. Worms appearing in cross-section are evident as hyperechoic roundish structures. Pleural effusion is seen as an echo-free (black) space external to the RA and RV. *LA*, left atrium; *LV*, left ventricle; *A*, ascending aorta; *IVS*, interventricular septum. (Courtesy of Dr. Dave Sisson.)

tial risk and severity of postadulticide complications are probably greater than the risks from spontaneous heartworm death and embolization in the asymptomatic cat. However, therapy with close post-treatment observation may be preferable in some cases compared with not knowing when the heartworms will die on their own if left untreated.

CONSERVATIVE THERAPY

In cases of intermittent clinical signs or when the potential risk of adulticidal therapy is not accepted, owners should be educated as to the nature of peracute signs related to heartworm embolization. Although alternate-day prednisolone (5 mg/kg) has been used successfully in some infected cats to treat coughing and vomiting, radiographic lesions usually progress, and acute respiratory distress and death are not prevented. An emergency dose of oral or injectable glucocorticoid should be dispensed for the owner to administer if collapse or dyspnea occurs.

The onset of acute respiratory signs in a heartworm cat is a true emergency requiring immediate care, including intranasal oxygen therapy, cage rest, small volumes of intravenous fluids, and injectable prednisolone. This therapy has improved clinical and radiographic signs within 24 hours in most cats with life-threatening dyspnea and collapse.

ADULTICIDE THERAPY

Thiacetarsamide sodium (2.2 mg/kg IV, bid, for 2 days) is generally tolerated without immediate complications of hepatotoxicity or renal toxicity.[3, 15, 37] Acute signs (collapse) have occurred after rapid thiacetarsamide injections, but slow administration is generally safely administered in my experience. Careful intravenous administration is essential and is facilitated by sedation. Because of the potential protective effects of ketamine as an serotonin antagonist, a single intramuscular injection has been recommended before the first dose of thiacetarsamide, also to assist in the latter's safe intravenous administration.

Pulmonary edema is an unpredictable but occasional complication during the 2 days of thiacetarsamide therapy. Oxygen therapy and corticosteroids should be considered if dyspnea or cyanosis occurs.

Clinical signs tend to improve after therapy. Cats with chronic anorexia require nutritional support. Although the presence of circulating microfilariae is uncommon, ivermectin (50 μg/kg) has been used successfully as a microfilaricide.

POSTADULTICIDE COMPLICATIONS

Based on the assumption that heartworm mass is related to antigen load,[38] a cat with a "strong positive" antigen test would be more likely to develop postadulticide complications than a cat that has a low worm burden and is antigen negative or "weakly positive."

Postadulticide reactions are peracute. This dictates that the cat be under constant surveillance, especially during the first 2 weeks.[3, 19] Complications are usually related to embolization, which can induce lung infarction, hemoptysis, and dyspnea. Severe thrombocytopenia has not been noted. Sudden death can occur within the first 10 days after thiacetarsemide administration.

Embolization most often affects the caudal lung lobes, which may be evident by increased radiographic density. Oxygen therapy is indicated if dyspnea occurs. High doses of corticosteroids (prednisolone, 1 mg/kg tid) with judicious intravenous fluid therapy are often helpful during this crisis. The clinical and radiographic signs of acute embolization can resolve over 1 to 2 days.

Routine use of corticosteroids or aspirin is not recommended before or after thiacetarsemide. Aspirin is contraindicated in feline heartworm disease. It may inhibit prostaglandin formation and thus increase pulmonary leukotriene production. This could increase inflammatory mediators and lead to bronchospasm and pulmonary hypertension.

ASSESSMENT OF ADULTICIDE TREATMENT EFFICACY

The efficacy of thiacetarsemide cannot be evaluated in many cases of occult feline heartworm disease. However, current research indicates that the adulticide is effective. Clinical signs usually abate during the initial weeks after its administration.[16, 19, 33]

Immature worms are probably resistant to thiacetarsemide in cats as in the dog. By serologic testing, if a cat was antigen positive before treatment, the antigen test should be negative 12 weeks after adulticide therapy. A positive test at this time would indicate the persistence of adult heartworms.

PREVENTIVE THERAPY

In highly endemic areas, the incidence of feline heartworm infections is high, and preventive therapy is indicated. In nonendemic areas, the incidence is not sufficient to warrant preventive therapy in cats.

Infection from *D. immitis* can be prevented with 50 μg/kg of milbemycin oxime (Interceptor, Ciba Geigy) or 25 μg/kg of ivermectin (Heartgard, Merial) administered per os once a month. In endemic areas, it is suggested that preventive medication be administered at 4 to 6 weeks of age and continued for the life of the cat. Because current antigen testing is unreliable in cats, antigen testing before instituting preventive therapy in an adult cat does not seem to be cost effective. Heartworm-positive cats can be placed on ivermectin without complications.

REFERENCES

1. Calvert CA. Feline heartworm disease. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 551
2. Dillon AR, Warner AE, Molina J. *Dirofilaria immitis* infection in dogs and cats results in pulmonary airway epithelial and microvascular injury. J Am Coll Vet Intern Med 7:119, 1993

2a. Manella C, Donoghue AR. Feline heartworm disease and its diagnosis. Feline Pract 26:5, 1998

3. Dillon AR. Feline heartworm disease. *In* Kirk RW (ed): Current Veterinary Therapy IX. Philadelphia, WB Saunders, 1986, p 420
4. Donahoe JM, Kneller SK, Lewis RD. In vivo pulmonary arteriography in cats infected with *D. immitis*. J Am Vet Radiol Soc 17:147, 1976
5. Donahoe JM, Holzinger EA. *D. immitis* in the brains of a dog and a cat. J Am Vet Med Assoc 164:518, 1974
6. Lillis WG. *D. immitis* in dogs and cats from south central New Jersey. J Parasitol 50:802, 1964
7. Mandelker L, Brutus RL. Feline and canine dirofilaria encephalitis. J Am Vet Med Assoc 159:776, 1971
8. Noyes JD. Illinois State Veterinary Medical Association Yearly Heartworm Survey. In Otto GF (ed): Proceedings, Heartworm Symposium. Bonner Springs, KS, Veterinary Medical Publishing Company, 1978, p 1
9. Seymore DN. Dirofilariasis in a cat. Mod Vet Pract 61:251, 1980
10. Sherman WA, Wechester SJ. Unusual case of heartworm disease in a cat. Vet Med/Small Anim Clin 70:1320, 1975
11. Stackhouse LL, Claugh E. Clinical report: Five cases of feline dirofilariasis. Vet Med/Small Anim Clin 67:1309, 1972
12. Soifer FK. Dirofilariasis in a cat. Vet Med/Small Anim Clin 71:484, 1976
13. Teske RH. Dirofilariasis in a cat. J Am Vet Med Assoc 159:891, 1971
14. Todd KS, Byerly CS, Small E, et al. Heartworm infections in Illinois cats. Feline Pract 6:41, 1976
15. Calvert CA, Mandell CP. Diagnosis and management of feline heartworm disease. J Am Vet Med Assoc 180:5650, 1982
16. Dillon AR, Sakas PS, Buxton BA, et al. Indirect immunofluorescence testing for diagnosis of occult *Dirofilaria immitis* infection in three cats. J Am Vet Med Assoc 180:80, 1982

16a. Atkins CE, DeFrancesco TC, Miller MW, et al. Prevalence of heartworm infection in cats with signs of cardiorespiratory abnormalities. J Am Vet Med Assoc 212:517, 1998

17. Hawe RS. The diagnosis and treatment of occult dirofilariasis in a cat. J Am Anim Hosp Assoc 15:577, 1979
18. Harlton BW. Treatment of dirofilariasis in a domestic cat. Vet Med/Small Anim Clin 69:1440, 1974
19. Schwartz A. Two cases of feline heartworm disease. Feline Pract 5:20, 1975
20. Byerly CS, Donahoe JMR, Todd KS. Histopathologic changes in cats experimentally infected with *Dirofilaria immitis*. *In* Otto GF (ed): Proceedings, Heartworm Symposium. Bonner Springs, KS, Veterinary Medical Publishing Company, 1977
21. Donahoe JR, Kneller SK, Lewis RE. Hematologic and radiographic changes in cats after inoculation with infective larvae of *D. immitis*. J Am Vet Med Assoc 168:413, 1976
22. Donahoe JM. Experimental infection of cats with *D. immitis*. J Parasitol 61:599, 1975
23. Fowler JL, Matsuda K, Fernan RC. Experimental infection of the domestic cat with *D. immitis*. J Am Anim Hosp Assoc 8:79, 1972
24. Pacheco G. Synopsis of Dr. Kume's report at the first international symposium on canine heartworm disease. *In* Bradely R (ed): Canine Heartworm Disease: Current Knowledge. Gainesville, FL, University of Florida Press, 1972, p 137
25. Rawlings CA, Losonsky JM, Lewis RE, et al. Response of the feline heart to Aelurostrongylus abstrusus. J Am Anim Hosp Assoc 16:573, 1980
26. Wong MM, Pedersen NC, Cullen J. Dirofilariasis in cats. J Am Anim Hosp Assoc 19:855, 1983
27. Dillon AR, Brawner WR, Grieve RB, et al. The chronic effects of experimental *Dirofilaria immitis* infection in cats. Sem Vet Med Surg (Small Anim) 2:72, 1987
28. Otto GF. Abnormal host—abnormal location. Am Heartworm Soc Bull 4:14, 1978
29. Otto GF. Occurrence of the heartworm in unusual locations and in unusual hosts. *In* Otto GF (ed): Proceedings, Heartworm Symposium 1974. Bonner Springs, KS, Veterinary Medical Publishing Company, 1974, p 6
30. Benard MA. Acute dirofilarial death. Can Vet J 11:190, 1978

31. Griffith HJ, Schlotthauer JC, Gehrman FW. Feline dirofilariasis. J Am Vet Med Assoc 140:61, 1962
32. Grieve RB, Mika-Johnson M, Jacobson RH, et al. Enzyme-linked immunosorbent assay for measurement of antibody responses to *Dirofilaria immitis* in experimentally infected dogs. Am J Vet Res 42:66, 1981
33. Green BJ, Lord PF, Grieve RB. Occult feline dirofilariasis confirmed by angiography and serology. J Am Anim Hosp Assoc 19:847, 1983
34. Calvert CA, Coulter DB. Electrocardiographic values for anesthetized cats in lateral and sternal recumbencies. Am J Vet Res 42:1453, 1981
35. Owens JM, Twedt DC. Nonselective angiocardiography in the cat. Vet Clin North Am 7:309, 1977
35a. Venco L, Calzolari D, Mazzocchi D, et al. The use of echocardiography as a diagnostic tool for detection of feline heartworm *(Dirofilaria immitis)* infections. Feline Pract 26:6, 1998
36. Suter PF, Lord PF. Radiographic differentiation of disseminated pulmonary parenchymal diseases in dogs and cats. Vet Clin North Am 4:687, 1974
36b. Borgarelli M, Venco L, Piza PM, et al. Surgical removal of heartworms from the right atrium of a cat. J Am Vet Med Assoc 211:68, 1997
37. Desowitz RS, Una SR. The detection of antibodies in human and animal filariasis by counterimmunoelectrophoresis with *D. immitis* antigens. J Helminth 50:53, 1976
38. Weil GJ, Malone MS, Powers KG, et al. Monoclonal antibodies to parasite antigens found in the serum of *Dirofilaria immitis*-infected dogs. J Immunol 2:1185, 1985

VI

Effects of Systemic and Metabolic Disorders on the Heart

32

Nutrition and Management of Cardiovascular Disease

PAUL D. PION
BRUCE W. KEENE
MATTHEW MILLER
PHILIP R. FOX

The importance of nutrition and heart disease has been underscored by recent advances in veterinary cardiology.[1] Previously, the intersection between nutrition and cardiology began and ended with concerns about dietary sodium content.[2–5] Today, the association between nutrition and cardiovascular biochemistry, energy production, and cardiac function is key to understanding several common acquired disorders.

Many nutritional therapeutic recommendations are derived from well-meaning but weakly supported sources. Thus, whenever administering drugs or prescribing nutritive pharmaceuticals or special diets, one must consider the source of information, strength of evidence presented, financial costs, and potential risks and benefits.

Current management of heart failure emphasizes an integrated approach.[1, 6] This involves systematic application of cardiac drug therapy (chapters 12, 17); assessment of dietary sodium balance;[7–10] awareness of clinical dietary effects, neuroendocrine system activation, and compensatory renal mechanisms;[11–18] attention to clinical assessment and monitoring;[19–21] and periodic evaluation of electrolytes and nutritional factors.[16, 22–26]

ROLE OF ELECTROLYTES IN CARDIOVASCULAR DISEASE

SODIUM

Total body sodium is determined by the balance between sodium intake and excretion. Passive and active carrier mechanisms effected by neuroendocrine control systems modulate total body sodium and sodium ion distribution between intracellular and extracellular compartments.[10]

With popularization of drugs that markedly affect sodium and water excretion (e.g., loop diuretics, angiotensin-converting enzyme inhibitors

[ACEI]), recommendations for severe sodium restriction in humans are changing.[6] Recent advances in the understanding of mechanisms by which sodium and water excretion are regulated may affect future dietary sodium recommendations.

NEUROHUMORAL AND HEMODYNAMIC EFFECTS OF SODIUM RESTRICTION

Plasma renin activity is significantly elevated in dogs fed a low-sodium diet.[13, 15] Maintenance of blood pressure in hyponatremic animals appears to depend more on renin-angiotensin-aldosterone system activity than sympathetic nervous system stimulation. Carotid baroreceptor reflexes were blunted in response to acute carotid sinus occlusion in normal dogs who were chronically sodium depleted.[15] Sodium-depleted dogs show a greater elevation in blood pressure in response to renal artery constriction than do sodium replete dogs. This elevation was reversed by ACEI drug administration.[17]

EFFECTS OF SODIUM RESTRICTION ON PLASMA SODIUM IN NORMAL DOGS

In normal dogs, the effect of low-sodium diets on plasma sodium concentration is unclear. "Significant" decreases in plasma sodium have been reported, although the exact magnitude of said decrease was unspecified.[13, 14] Others report no significant change in plasma sodium in normal dogs fed low-sodium diets.[15, 16]

Chronic sodium restriction of normal dogs caused significantly decreased cardiac output, stroke volume, and plasma volume and significantly increased heart rate and peripheral vascular resistance. These effects were fully reversed with change to a sodium replete diet.[11]

EFFECTS OF SODIUM RESTRICTION IN CONGESTIVE HEART FAILURE

Dietary sodium restriction has long played a role in management of human cardiovascular diseases,[6] although the consequences of sodium restriction have not been fully explored in animals with congestive heart failure (CHF). In dogs with experimentally induced CHF, significant changes in plasma volume, sodium excretion, and voluntary water intake were not reflected by significant changes in plasma sodium. This suggests that plasma sodium concentration may be an insensitive index of sodium and water balance in CHF.[18] Low-sodium diets have been recommended in veterinary medicine to decrease sodium delivery to the distal tubule and thereby reduce "facultative reabsorption" of distal renal tubular sodium.[1] Compared with normal dogs, an impaired ability to excrete dietary sodium has been reported in dogs with naturally occurring CHF, with asymptomatic cardiac disease, and with heart failure due to experimentally induced valvular disease.[20] Early studies demonstrated that low-sodium intake was clinically beneficial in some unmedicated dogs with asymptomatic heart disease and in some with CHF; however, the number of dogs evaluated was small.[3] Some investigators have stated that sodium intake in dogs with CHF could be safely restricted to "any level required to relieve congestion."[4]

HYPONATREMIA

Hyponatremia is associated with increased morbidity and mortality in humans with heart failure.[5] Although it is uncommon for hyponatremic patients with CHF to be sodium depleted,[7, 8] a number of factors may contribute to dilutional hyponatremia via retention of free water and increased thirst. These include (1) renin-angiotensin-aldosterone system activation, (2) antidiuretic hormone (ADH) secretion, (3) local renal factors (tubular flow kinetics), and (4) diuretics.[9] Hyponatremia may result in neurologic signs due to decreased plasma osmolality. When accompanied by dehydration, signs of low cardiac output may occur.[10]

Although hyponatremia may result from heart failure or related therapy in some dogs and cats, it does not occur in all cases, even when patients with similar disease severity are treated with the same drugs.[7] Low serum-sodium concentration has been correlated with increased plasma norepinephrine levels in humans with CHF[11] and in dogs with severe CHF due to dilated cardiomyopathy.[12] Hyponatremia with heart failure confers a poor prognosis.[7]

CLINICAL APPLICATION OF DIETARY SODIUM RESTRICTION

Traditionally, sodium restriction has been recommended by veterinarians for animals with heart disease. This has included homemade diets prepared by owners (Table 32–1)[22] or commercial pet foods formulated as prescription diets (Table 32–2).[26a] The intent of restricting dietary sodium is to reduce sodium and water retention, thereby decreasing cardiac preload.[1–4] Although common sense and theory dictate avoidance of high-sodium intake in dogs and cats with heart failure, virtually no data demonstrate or refute a true clinical advantage to feeding sodium-restricted over routine maintenance diets. When overt CHF is present, dietary sodium restriction seems rational if the diet is accepted by the pet.[1, 2, 20, 21]

Sodium restriction represents one of the many components of heart failure management but should not be aggressively pursued at the expense of caloric in-

TABLE 32-1
Recipes for Homemade Diets for Dogs and Cats with Cardiac Disease

Highly Digestible Diet for Dogs		Low-Sodium Diet for Dogs		Restricted Mineral and Sodium Diet for Cats	
Balanced supplement that fulfills the canine minimum daily requirement for all vitamins and trace minerals: ½ cup farina cooked to make 2 cups 1½ cups creamed cottage cheese (low salt) 1 large egg, hard-cooked 2 tbsp brewer's yeast 3 tbsp sugar 1 tbsp vegetable oil 1 tsp potassium chloride 1 tsp dicalcium phosphate 1 tsp calcium carbonate		Balanced supplement that fulfills the canine minimum daily requirement for all vitamins and trace minerals: ¼ lb lean ground beef or pork or chicken 2 cups cooked rice without salt 1 tbsp vegetable oil 2 tsp dicalcium phosphate		Balanced supplement that fulfills the feline minimum daily requirement for all vitamins and trace minerals: 1 lb regular ground beef or lamb or chicken cooked ¼ lb liver 1 cup cooked rice without added salt 1 tsp vegetable oil 1 tsp calcium carbonate	
Cook farina according to package directions, omitting salt. Cool. Add remaining ingredients to farina and mix well.		Braise meat, retaining fat. Add the remaining ingredients and mix.		Combine all ingredients.	
Yield: 2.2 lb (1 kg)		Yield: 1 lb (0.5 kg)		Yield: 1¾ lb (0.8 kg)	
Analysis		**Analysis**		**Analysis**	
Moisture %	75.8	Moisture %	68.5	Moisture %	64.0
Protein %	7.1	Protein %	6.3	Protein %	14.1
Fat %	3.7	Fat %	5.5	Fat %	13.8
Carbohydrate %	11.2	Carbohydrate %	17.7	Carbohydrate %	6.6
Fiber %	0.1	Sodium %*	.01	Ash %	1.5
Ash %	2.1	ME (Kcal)	660/lb	Calcium %	0.24
Calcium %	0.33			Phosphorus %	0.15
Phosphorus %	0.19			Magnesium %	0.014
Potassium %	0.36			Magnesium, mg/100 Kcal	8
Sodium %	0.16			Sodium %	0.06
ME (Kcal)	485/lb			ME (Kcal)	940/lb

*50 mg sodium/100 g dry diet. ME, metabolizable energy as fed.
Modified from Lewis LD, Morris ML Jr (eds). Small Animal Clinical Nutrition. 3rd ed. Topeka, KS, Mark Morris Associates, 1987, p A3-1.

take. In general, a less sodium-restricted, more palatable diet is better than a more sodium-restricted diet that a pet refuses to eat. Excessive sodium restriction alone or in combination with certain cardiac drugs such as diuretics and ACE inhibitors can occasionally affect the patient adversely. The potential for hyponatremia and azotemia increases when dietary sodium restriction is combined with high doses of loop diuretics such as furosemide.

POTASSIUM

Electrolytes other than sodium are also important concerns in patients with heart disease. High dosages of potent diuretics, most notably the loop diuretics such as furosemide and bumetanide, may cause hypokalemia and hypomagnesemia. This is especially true when patients are anorectic.

HYPOKALEMIA

Hypokalemia is the most common electrolyte abnormality encountered during heart failure therapy in humans.[23] Contributory factors include reduced potassium intake associated with anorexia, diuretic-induced renal potassium loss, hyperaldosteronism, and persistent chloride depletion. Whereas high-sodium diets increase delivery of sodium chloride to the distal tubular potassium-secreting sites, very-low-sodium diets may stimulate aldosterone-induced potassium secretion.

The incidence of hypokalemia in dogs and cats being treated with diuretics for CHF is not known. One study[24] documented a clinically insignificant drop in serum potassium in dogs treated chronically with furosemide. A large multicenter investigation studying canine heart failure revealed no clinically significant serum electrolyte changes in dogs treated with furosemide and enalapril.[26a] Severe hypokalemia in diuretic-treated animals is rare, but significant hypokalemia can occur,[25] especially in cats (chapter 28). Therefore, serum potassium should be monitored in animals at increased risk for developing hypokalemia.

Hypokalemia causes increased morbidity in heart failure patients and the need for potassium replacement therapy.[26] Animals in CHF are frequently at risk for ventricular arrhythmias and often receive digitalis glycosides. The enhanced automaticity of cardiac tissue in response to toxic levels of digoxin is increased by hypokalemia.[27] Also, the efficacy of class I antiarrhyth-

TABLE 32–2
Sodium, Potassium, and Magnesium Content of Selected Commercial Animal Foods

	Sodium (%)*	Potassium (%)*	Magnesium (%)*
Popular Dry Dog Foods			
Mean	0.40	0.69	0.17
High	0.68	0.99	0.30
Low	0.12	0.48	0.10
Purina Dog Chow	0.42	0.67	0.16
Alpo Beef Dinner	0.36	0.82	0.28
Gaines Gravy Train	0.40	0.80	0.16
Friskies Come 'N Get It	0.55	0.59	0.14
Purina Hi-Pro Dog Meal	0.38	0.50	0.13
Kal Kan Pedigree Meal Time	0.68	0.58	0.16
Purina Kibbles 'N Chunks	0.29	0.75	0.16
Field Trial Chunks	0.48	0.76	0.30
Gaines Cycle-2 Adult	0.14	0.99	0.19
Gaines Cycle-4 Senior	0.12	0.80	0.21
Purina O.N.E. Adult	0.50	0.54	0.10
Purina O.N.E. Lite	0.49	0.48	0.10
Premium/Super Premium Dry Dog Foods			
Mean	0.35	0.65	0.11
High	0.54	0.86	0.15
Low	0.18	0.36	0.08
Iams Less Active	0.26	0.75	0.12
Iams Chunks	0.54	0.86	0.10
Iams Eukanuba Adult	0.33	0.80	0.08
Nutro Max	0.48	0.60	0.13
Purina Pro Plan Adult	0.41	0.55	0.10
Purina Pro Plan Lite	0.42	0.44	0.10
Hill's Science Diet Canine Maintenance	0.27	0.63	0.12
Hill's Science Diet Canine Maintenance Light	0.24	0.84	0.15
Hill's Science Diet Canine Senior	0.18	0.36	0.11
Popular Canned Dog Foods			
Mean	0.99	1.32	0.08
High	1.61	1.96	0.14
Low	0.51	0.75	0.04
Alpo Beef Chunks Dinner	0.64	1.32	0.07
Kal Kan Pedigree with Chunky Beef	1.38	1.08	0.04
Mighty Dog Pure Beef	1.02	1.23	0.04
Kal Kan Grand Gourmet with Chunky Beef	1.19	1.96	0.08
Gaines Cycle-2 Adult	0.60	1.64	0.09
Skippy Chunky Beef Dinner	0.96	1.46	0.14
Quaker Oats King Kuts with Real Beef	1.01	1.10	0.06
Ken-L-Ration Original	1.61	1.57	0.13
Kal Kan Pedigree Select Dinner	1.40	1.26	0.10
Recipe Chunky Beef Stew	0.53	1.15	0.09
Cadillac Chunky Beef Dinner	0.51	0.75	0.05

mic drugs (e.g., lidocaine, procainamide, quinidine) is markedly diminished by hypokalemia.[28] Although hypokalemia is commonly associated with heart failure and diuretic therapies, serum potassium may increase with concomitant administration of certain prostaglandin synthetase inhibitors, β-adrenergic blockers, potassium-sparing diuretics, and angiotensin-converting enzyme inhibitors.[25, 29]

MANAGEMENT OF HYPOKALEMIA. Decisions regarding potassium supplementation are based on serum electrolyte levels. Empiric therapy with oral potassium agents should be avoided. In situations of critical hypokalemia, potassium replacement can be accomplished through judicious intravenous (IV) fluid administration, avoiding excessive fluid administration (preload) and exacerbation of heart failure; IV potassium should not be administered faster than 0.5 mEq/kg/hr. Preferably, potassium can be supplemented orally using commercial replacement products, or by force feeding through nasoesophageal (cats) or pharyngeal (dogs) tubes.

EFFECTS OF ACE INHIBITORS ON PLASMA SODIUM AND POTASSIUM

A large multicenter trial studying the effects of enalapril in dogs with chronic acquired valvular disease

TABLE 32–2
Sodium, Potassium, and Magnesium Content of Selected Commercial Animal Foods *Continued*

	Sodium (%)*	Potassium (%)*	Magnesium (%)*
Premium/Super Premium Canned Dog Foods			
Mean	0.38	0.76	0.11
High	0.54	1.45	0.17
Low	0.26	0.37	0.08
Hill's Science Diet Canine Maintenance	0.29	0.62	0.12
Hill's Science Diet Canine Maintenance Light	0.35	0.58	0.12
Hill's Science Diet Canine Senior	0.26	0.44	0.09
Iams Beef Formula	0.33	0.73	0.10
Iams Turkey Formula	0.54	0.69	0.08
Iams Chicken Formula	0.47	0.75	0.12
Iams Lamb & Rice Formula	0.44	0.80	0.12
Nature's Recipe Maintenance Lamb & Rice	0.50	1.45	0.17
Nutro Max Chicken, Lamb & Rice	0.26	0.72	0.08
Nutro Natural Choice Lamb & Rice	0.39	0.78	0.09
Dietary Animal Foods			
Mean	0.21	0.69	0.09
High	0.55	1.15	0.14
Low	0.08	0.30	0.05
Hill's Prescription Diet Canine h/d dry	0.08	0.72	0.12
Hill's Prescription Diet Canine h/d canned	0.08	0.83	0.13
Hill's Prescription Diet Canine k/d dry	0.23	0.38	0.08
Hill's Pescription Diet Canine k/d canned	0.22	0.30	0.08
Hill's Prescription Diet HealthBlend Canine Adult dry	0.22	0.54	0.08
Hill's Prescription Diet HealthBlend Canine Adult canned	0.22	0.49	0.09
Hill's Prescription Diet HealthBlend Canine Geriatric dry	0.17	0.45	0.10
Hill's Prescription Diet HealthBlend Canine Geriatric canned	0.26	0.37	0.09
Hill's Prescription Diet Feline k/d canned	0.28	0.93	0.05
Hill's Prescription Diet Feline k/d dry	0.25	0.89	0.05
Pro-Visions CNM CV-Formula canned	0.15	1.15	0.08
Waltham low sodium diet canned	0.22	1.07	0.10
Theradiet Heart canned	0.11	0.40	0.05
Neura H diet canned	0.11	0.94	0.09
Cadillac Special Formulation Diet H canned	0.55	0.82	0.14

*Nutrient content calculated as a percentage of diet dry matter.
From Roudebush P. Strategies for avoiding diet-drug interactions in dogs with cardiac disease and in dogs with cardiac disease and failure. Vet Med 89(7)(Suppl):714–723, 1994, with permission.

(endocardiosis) and dilated cardiomyopathy found no clinically significant serum electrolyte abnormalities. Moreover, the prevalence of azotemia in both placebo- and enalapril-treated animals was not significantly different.[29a] Many of these dogs were fed commercial sodium-restricted diets.

MAGNESIUM

Magnesium depletion has received growing attention as a potential contributor to cardiovascular morbidity in dogs[29b, c] and humans with CHF.[30–31a] Urinary magnesium wasting occurs with both thiazide and loop diuretic therapy, unlike urinary calcium excretion, which is enhanced only by loop diuretics.[32] Magnesium deficiency in humans results most commonly from poor dietary magnesium intake and increased renal magnesium wasting. The latter is generally due to diuretics or drugs that exacerbate renal magnesium loss (e.g., ethyl alcohol, *cis*-platinum, amphotericin B, and certain aminoglycoside antibiotics). Digitalis toxicity can be exacerbated by hypomagnesemia,[27] and digitalis may also potentiate renal magnesium wasting.[33] Hypomagnesemia appears to be present in some dogs with heart disease.[29b, c]

Serum magnesium does not usually correlate well with tissue concentrations. Magnesium is largely bound to intracellular buffers or to bone, with only approximately 1 percent residing in the extracellular space.[34] More reliable than serum magnesium levels are magnesium assays from skeletal and cardiac muscle biopsies, or measurements of free or total magnesium in circulating mononuclear cells.[35] Unfortunately, these tests are not readily available. Serial measurements of serum magnesium in a given patient may reflect changes in total body magnesium homeostasis.

MANAGEMENT OF HYPOMAGNESEMIA. Magnesium replacement therapy is usually considered when (1)

there is high clinical suspicion of deficiency, as may occur in a cachectic chronic heart failure patient receiving digoxin and loop diuretics, and (2) a low-normal serum magnesium level is detected. Some ventricular arrhythmias in humans have responded favorably to magnesium supplementation, even in the face of normal serum magnesium levels.[36]

CARDIAC CACHEXIA

Cardiac cachexia has been recognized for centuries[37] and refers to loss of total body fat and lean body mass, most notably skeletal muscle. In dogs it usually accompanies severe chronic CHF. In cats it is relatively uncommon but, when observed, is generally seen with chronic, severe, right-sided CHF. In humans, cardiac cachexia, as defined by anthropometry and low serum albumin, is present in 35 to 50 percent of patients with severe, chronic CHF.[38] Protein-energy malnutrition *(kwashiorkor)* and total body malnutrition *(marasmus)* have been used to describe different clinical conditions in humans.[38a]

PATHOPHYSIOLOGY

Although no unified concept explains the pathogenesis of cardiac cachexia, a number of factors may contribute.[39, 40] Decreased caloric intake, reduced caloric assimilation, increased caloric utilization, hormonal changes, altered balance between catabolism and anabolism, and iatrogenic causes have been proposed.

INAPPETENCE AND ANOREXIA

Inadequate intake of calories and vitamins has been documented in human heart failure patients.[41] Mild abdominal discomfort associated with ascitic distention is common in humans with right-sided heart failure and may act as a deterrent to eating, especially if eating intensifies the discomfort. Gastric compression by ascitic fluid and hepatomegaly may simulate satiety or fullness. Reduced gastric emptying associated with altered gastric motility has been described.[42] A common observation in animals is that diets are made unpalatable by severe sodium and protein restriction.

MALABSORPTION AND MALDIGESTION

Significant steatorrhea has been demonstrated in 56 percent of humans with right-sided heart failure, and a number of these patients may suffer from a primary digestive defect.[13] Intestinal mucosal congestion may contribute to malabsorption. Pancreatic edema may cause functional pancreatic cellular impairment or blockage of acini leading to maldigestion. Others have documented protein-losing enteropathy from secondary intestinal lymphangiectasia associated with tricuspid regurgitation.[44] Lymphangiectasia from systemic venous hypertension and lymphatic hypertension not only causes gastrointestinal protein loss, it is also associated with loss of lymphocyte-rich lymph and resultant immunologic impairment.

SYSTEMIC VENOUS CONGESTION

The nutritional status in cardiac cachexia may be influenced more by systemic venous congestion than by reduced cardiac output. Higher right atrial pressures and more severe tricuspid regurgitation have been noted in patients with malnutrition and cardiac cachexia than in those with normal nutritional status.[38, 44] The importance of increased right atrial pressure is supported by the finding of protein-losing enteropathy in patients with constrictive pericardial disease[45] and congenital right atrial lesions,[46] in which left ventricular systolic function may be normal.[44]

HYPERMETABOLISM

Abnormal energy expenditure accelerates the wasting process. An absolute or relative degree of hypermetabolism may result from increased myocardial oxygen consumption, hyperpnea, increased work of breathing, and, occasionally, low-grade fever.[47–49] Sympathetic nervous system activation associated with chronic CHF[12, 50] may contribute to the hypermetabolism associated with cardiac cachexia.

DRUG TOXICITIES

Drugs such as digitalis glycosides and some ACEI such as captopril may cause direct toxicity and untoward gastrointestinal effects. Digitalis glycosides also exert an inhibitory effect on sugar and amino acid transport in the small bowel.[51] Plasma electrolytes may become altered by cardiac glycosides, ACEI, and diuretics, affecting appetite and gastrointestinal motility.

TUMOR NECROSIS FACTOR

Tumor necrosis factor (TNF) has been implicated in the pathogenesis of cardiac cachexia. Also referred to as cachectin, TNF is a cytokine produced primarily by monocytes. It has cytotoxic activity against certain tumor cells and inhibits activity of lipoprotein lipase, an enzyme involved in the hydrolysis of chylomicron-associated triglycerides to free fatty acids and glycerol.[52, 52a]

Clinical studies have documented elevated circulating TNF levels in cachectic humans and canines with chronic heart failure,[53–55] and in some cats with heart

failure.[55a] In humans, TNF levels were most elevated in patients who had high plasma renin activity, low serum sodium concentration, and poor renal function. Renin and prostaglandin (especially prostaglandin E_2) are released in chronic CHF to regulate glomerular filtration and systemic vascular resistance. Concentrations of prostaglandin E_2 similar to those measured in patients with hyponatremic heart failure stimulate TNF production from monocytes *in vitro*.[56, 57]

MANAGEMENT OF CARDIAC CACHEXIA

Cardiac cachexia is debilitating, leading eventually to severe skeletal muscle wasting and a poor prognosis. Management includes (1) assuring adequate caloric intake, (2) drug therapy to improve hemodynamic parameters affected by heart failure, and (3) avoidance of drug toxicities or unpalatable diets that contribute to anorexia. Future interventions might include attempts to alter elevated circulating TNF levels. For example, both oxpentifylline and n-3 polyunsaturated fatty acids suppress TNF concentrations in humans.[58]

ARTERIAL HYPERTENSION AND DIET

Elevation of arterial blood pressure and associated conditions are receiving increasing attention (chapter 35). The roles of certain nutrients are being explored, and dietary modifications are often included in therapy. Dietary management of systemic hypertension has largely been limited to dietary sodium restriction.[1, 2, 22, 59]

SODIUM CHLORIDE

Excessive dietary sodium intake has been incriminated in the pathogenesis of human primary hypertension. Most commercial dog foods contain high levels of sodium chloride, some in excess of 1 percent on a dry weight basis (Table 13–2).[22, 26a] Experimentally, arterial blood pressure may return to normal with dietary sodium chloride restriction in some animal models and in many humans with hypertension secondary to renal disease.[60] It is presumed that dogs and cats with hypertension associated with renal disease would benefit from moderate dietary sodium restriction. Sodium intakes between 0.1 and 0.3 percent of the diet have been recommended for dogs and 0.4 percent of the diet recommended for cats.[17, 22, 59]

OMEGA – 3 FATTY ACIDS

Fish oils and other seafoods contain a special class of polyunsaturated fatty acids called omega (ω) -3, or n $-$ 3 ("n minus three"), fatty acids. They have been reported to exert certain antihypertensive effects[61, 62] and possibly to reduce mortality from coronary disease in humans, although recent findings[62a] have shown limited promise for the latter. Prostaglandins and other eicosanoids from polyunsaturated fatty acids affect blood pressure regulation.[63] Alterations in blood pressure during dietary supplementation with $\omega - 3$ fatty acids may be due to changes in endogenous synthesis of vasoactive eicosanoids.[61]

Other possible mechanisms have been proposed. For example, $\omega - 3$ fatty acids might enhance the renal handling of electrolytes; effect the release or response to renin and related hormones;[64] protect renal function by lowering arterial pressure and reducing the progressive renal dysfunction with systemic hypertension; and reduce vascular responsiveness to systemic vasoconstrictors and a lower blood viscosity.[64] The effects of $\omega - 3$ fatty acids are not likely limited to altered renal function but may also involve vasoactive hormones or vascular reflexes.[65]

Ongoing veterinary studies evaluating the effect of dietary lipids on renal disease in dogs may provide insight.[66] Specific recommendations await further evaluations.

L-CARNITINE DEFICIENCY

L-Carnitine (3-hydroxy, 4-*N*-trimethylaminobutyric acid) is a small, water-soluble quaternary amine (molecular weight, 160), found in high concentrations in mammalian heart and skeletal muscle. In the dog, L-carnitine is synthesized from the amino acids lysine and methionine. The enzyme required for final synthesis, gamma-butyrobetaine hydroxylase, is found primarily in the liver but not in mammalian heart or skeletal muscle.

ROLE OF L-CARNITINE IN CANINE DILATED CARDIOMYOPATHY

A poorly understood membrane transport mechanism concentrates L-carnitine in cardiac and skeletal myocytes. In normal mammals, plasma carnitine correlates closely with myocardial carnitine concentrations. This close correlation is lost in canine dilated cardiomyopathy (DCM). Pathophysiology, metabolism, and deficiency states have been reviewed.[67–78]

PHYSIOLOGIC FUNCTIONS OF CARNITINE

MYOCARDIAL ENERGY PRODUCTION

Free carnitine is required in the myocardium for fatty acid metabolism, and it serves an important detoxifying role in the mitochondria.[67] Under all but immediate postprandial conditions, long-chain free fatty acids are quantitatively the most important metabolic substrate for myocardial energy production. Carnitine is a critical component of the mitochondrial membrane enzymes (carnitine acetyl transferase I and II) that transport activated fatty acids in the form of acylcarnitine esters across the mitochondrial membranes to the matrix, where β-oxidation and subsequent high-energy phosphate generation occurs.

MITOCHONDRIAL DETOXIFYING ROLE

Free carnitine serves as a mitochondrial detoxifying agent by accepting (or "scavenging") acyl groups and other potentially toxic metabolites and transporting them out of the mitochondria as carnitine esters. Many defects in mitochondrial metabolism result in the toxic accumulation of these substances. For example, propri-onyl-CoA (coenzyme A) decarboxylase deficiency (one of the so-called organic acidurias) causes the toxic accumulation of proprionyl-CoA in mitochondria unless free carnitine is available to form a proprionyl-carnitine ester (which is excreted in the urine) and regenerate metabolically useful free CoA.[68] Similarly, defects in mitochondrial medium, long-chain, or multiple acylCoA dehydrogenase enzymes can cause acyl-CoA to accumulate in the mitochondria to toxic levels unless the excess acyl groups are esterified to free carnitine, producing an acyl-carnitine ester and regenerating free CoA. Excess carnitine esters cannot be reabsorbed by the kidney. Carnitine deficiency eventually results if large quantities of free carnitine are not supplied. Mitochondrial toxin build-up can be largely prevented if adequate free carnitine is available. However, underlying mitochondrial defect(s) are not corrected by carnitine supplementation, and carnitine therapy in these instances is palliative.

DIAGNOSIS: CANINE CARNITINE DEFICIENCY

A variety of clinical signs have been reported,[69] including encephalopathy, muscle weakness, recurrent infections, "failure to thrive," and congestive heart failure.[70] Carnitine deficiency has been associated with primary myocardial diseases in humans, hamsters, turkeys, and a family of boxer dogs.[71–74] American cocker spaniels with DCM and taurine deficiency may be responsive to taurine and L-carnitine therapy.[101]

ENDOMYOCARDIAL BIOPSY

Tissue biopsies are needed to document tissue carnitine deficiency definitively. Currently, transvenous endomyocardial biopsy is the best-tested method. This is performed in sedated dogs placed in lateral recumbency under fluoroscopic control. Generally considered a research technique, the procedure is not difficult or risky in experienced hands.[72]

CARNITINE ASSAYS AND NORMAL CANINE VALUES

Methods for measuring plasma and tissue carnitine concentrations have been described.[73] Appropriate samples (1 ml of heparinized plasma that was immediately separated and frozen; two 5-mg endomyocardial biopsy specimens acquired by standard techniques, blotted dry, and frozen in liquid nitrogen within 15 seconds of acquisition) may be sent to commercial or research laboratories for analysis. The cost of a plasma carnitine assay ranges from approximately $60 to $130 per sample. Tissue assays generally cost approximately twice as much.

Canine values for normal total, free, and esterified carnitine concentrations in plasma and myocardium are listed (Table 32–3). These are similar to values reported from larger, more invasive (open chest) dog studies.[74]

CARNITINE DEFICIENCY STATES: CLASSIFICATION

An absolute decrease in the plasma-free carnitine concentration is termed "plasma carnitine deficiency." Similarly, "myocardial carnitine deficiency" is diagnosed when the myocardial carnitine concentration falls below the 95 percent confidence interval for normal. In humans, when the ratio of esterified to free carnitine in plasma exceeds 0.4 in the face of normal

TABLE 32–3
Normal Canine Plasma and Myocardial Carnitine Concentrations*

Plasma Carnitine (μM/liter)			Myocardial Carnitine (nM/mg Noncollagenous Protein)		
Total	*Free*	*Esterified*	*Total*	*Free*	*Esterified*
12–38	8–36	0–7	5–13	4–11	0–4

*Ninety-five percent confidence intervals from six healthy dogs fed a standard commercial diet.

plasma concentrations of free carnitine, *carnitine insufficiency* is said to exist.[75] The utility of this ratio has not been extensively investigated in dogs. If both plasma and tissue free carnitine concentrations are decreased, *systemic carnitine deficiency* is present. When endomyocardial biopsy specimens contain decreased free carnitine despite normal or elevated plasma free carnitine concentrations, *myopathic carnitine deficiency* is present.

RELATIONSHIP BETWEEN PLASMA AND MYOCARDIAL CARNITINE CONCENTRATIONS

Plasma carnitine deficiency is a specific but insensitive marker for myocardial carnitine deficiency in dogs with DCM. Most (80 percent) of the dogs in whom myocardial carnitine deficiency has been identified have myopathic carnitine deficiency (see earlier), with normal or elevated plasma carnitine concentrations. Systemic carnitine deficiency is present in approximately 20 percent of the DCM cases. Current investigations at North Carolina State University estimate (using a 95 percent confidence interval constructed from 20 consecutive, unrelated dogs) that myocardial free carnitine deficiency occurs in between 19 and 95 percent of dogs with DCM, although plasma carnitine levels may be normal, elevated or low. Experimentally, chronic rapid ventricular pacing in dogs induces systolic myocardial dysfunction and CHF. This is also associated with myocardial carnitine deficiency in the face of normal or elevated plasma carnitine concentrations.[76]

MECHANISMS OF CARNITINE DEFICIENCY

Several potential factors may contribute to carnitine deficiency in canine DCM: (1) decreased carnitine synthesis; (2) decreased dietary intake (despite endogenous carnitine synthesis, dogs require a dietary carnitine source to maintain plasma carnitine concentrations at levels comparable to those found in other mammalian species because of their relatively limited renal capacity to reabsorb carnitine); (3) intestinal malabsorption; (4) increased renal loss; (5) abnormally increased esterification of free carnitine; and (6) myocardial membrane transport defects.[77] Because approximately 80 percent of the dogs with DCM that are fed commercial diets have myocardial carnitine deficiency with normal or elevated plasma carnitine concentrations, it is theorized that dogs might suffer from a membrane transport defect preventing adequate quantities of carnitine from entering the myocardium from the plasma.

CARNITINE THERAPY IN CANINE DILATED CARDIOMYOPATHY

INDICATIONS

Ideally, carnitine supplementation should be based on the documented presence of myocardial carnitine deficiency (Table 32–3). Unfortunately, endomyocardial biopsy is generally unavailable. Plasma carnitine concentrations offer a specific but insensitive indicator of myocardial carnitine deficiency, with limited utility in identifying carnitine-deficient patients. Recommendations for L-carnitine therapy in canine DCM are based upon a number of considerations: (1) myocardial carnitine may be increased following oral supplementation; (2) increased myocardial carnitine concentrations have been documented with dramatic clinical and hemodynamic improvement in a few dogs (primarily boxers receiving carnitine, and American cocker spaniels receiving taurine and carnitine); (3) the relative safety of this compound; and (4) the rationale that some clinical benefit may be derived from correcting this deficiency.

L-Carnitine is probably a useful adjunct to conventional pharmacotherapy in the treatment of heart failure for many, but by no means all, dogs with myocardial carnitine deficiency associated with DCM. There is no evidence that high doses have any effect in the absence of myocardial carnitine deficiency.

CLINICAL RESPONSE TO CARNITINE THERAPY

The efficacy of carnitine supplementation on survival or any objective parameter of myocardial function is difficult to measure. The natural progression of DCM is variable, and multiple drugs are used to manage associated CHF and arrhythmias.

Myocardial carnitine deficiency may represent only part of a spectrum of deleterious biochemical changes caused by many of the mitochondrial defects that contribute to DCM. Therefore, carnitine supplementation only imperfectly palliates these defects. This palliation may nevertheless be metabolically useful to the damaged myocardium, especially since it is obtained without the potential metabolic or hemodynamic "penalties" often associated with many conventional therapies. In a prospective pilot study, 18 Doberman pinschers with severe CHF and DCM received carnitine supplementation regardless of initial myocardial carnitine concentration. Dogs with myocardial carnitine deficiency survived significantly longer than those that had normal carnitine concentrations.[78] Although the therapeutic efficacy of carnitine per se was not tested, the mean survival of Dobermans with myocardial carnitine deficiency treated with carnitine in addition to conventional pharmacotherapy was substantially improved. In a blind, placebo-controlled trial, carnitine supplementation has been beneficial in the therapy of moderately severe human heart failure.[79] Carnitine has also been useful in treating CHF in Syrian hamsters[80] and American cocker spaniels.

The relatively small percentage of dogs that respond dramatically to carnitine therapy do so in a reasonably predictable manner:

1. The first notable observation is usually generalized clinical improvement. This includes increased appetite and activity, typically 1 to 4 weeks after initiation of oral carnitine supplementation.
2. Echocardiographic improvement is not generally demonstrable during the first 8 to 12 weeks of supplementation, and it may not occur at all. When observed, improvement in systolic time intervals and fractional shortening begins after 2 to 3 months of supplementation. Improvement may continue for about 6 to 8 months, when a plateau is often reached at which the dog appears clinically well despite depressed echocardiographic ventricular function indices (fractional shortening rarely improves above 15 to 25 percent).
3. The frequency and severity of ventricular ectopy generally remain unaltered by carnitine therapy.
4. Conventional heart failure therapy can occasionally be withdrawn from dogs responding to carnitine supplementation.

DOSAGE. Orally administered L-carnitine is rapidly and completely absorbed. Plasma concentrations following a single oral dose remain elevated for approximately 8 hours in the dog.[72] In DCM dogs with myocardial carnitine deficiency, high doses of carnitine (50 to 100 mg/kg tid) given orally elevate the plasma L-carnitine concentration 10 to 20 times above pretreatment values.[71] This usually (but not always) increases myocardial L-carnitine concentrations into the normal range, as demonstrated by endomyocardial biopsy findings following 1 to 3 months of therapy. If endomyocardial biopsy is unavailable, and the owner is comfortable with the financial expenditure relative to the uncertain benefits, carnitine supplementation is recommended. Large dogs (25 to 40 kg) receive 2 grams (approximately 1 teaspoonful of commercially available L-carnitine) mixed with food three times daily.

SAFETY. Carnitine appears to be extremely safe. Supraphysiologic doses have not produced serious adverse effects. Mild diarrhea has occasionally been reported in humans and one dog. The compound is widely available in health food stores without a prescription. Carnitine is classified by the FDA as a "medicinal food," and it is widely added to carnitine-poor foods for humans without an adequate source of carnitine and uncertain synthetic capabilities (e.g., nearly all infant feeding formulas are now supplemented with carnitine).

Only the L-isomer must be administered, since D-carnitine inactivates carnitine-containing enzyme systems, and mammals have no endogenous ability to convert D-carnitine to L-carnitine. Neither D-carnitine nor the racemic mixture (D-L-carnitine) can be safely administered.

CARNITINE DEFICIENCY AND CATS

Currently, no data implicate carnitine deficiency in feline myocardial disease, although little research in this area has been performed. Plasma carnitine concentrations measured from cardiomyopathic cats were generally higher than normal; myocardial concentrations were not investigated.[78a] Correlation between plasma and myocardial carnitine concentration is inconsistent.[78]

NORMAL FELINE CARNITINE VALUES

Mean carnitine concentrations were higher in adult cats than in kittens for skeletal muscle (total and free carnitine) and myocardium (free carnitine). Plasma carnitine was similar between genders in kittens; however, adults displayed higher total, free, and esterified carnitine concentrations in females than in males.[81] Normal values are listed in Table 32–4.[78]

TAURINE DEFICIENCY

Taurine (2-aminoethanesulfonic acid) is a sulfur-containing amino acid found throughout phylogenetic history. It is largely confined to animals and seldom encountered in plants.[82]

The majority of taurine is intracellular, dissolved in the cytosolic fluid and bound to cell membranes. Tissues with the highest taurine concentrations include heart, retina, central nervous system, and skeletal muscle.[83] In cats, intracardiac taurine concentrations range between 6 and 18 mM (compare with potassium—150 mM; and calcium—0.0001 mM in diastole, 0.01 mM in systole).[82, 84, 85] Taurine is also present in high concentrations in white blood cells and platelets.[86, 87] These high tissue taurine concentrations are maintained by active transport of taurine from plasma to the intracellular space that is modulated by the β-adrenergic receptor–adenylate cyclase system.[88]

PHYSIOLOGIC ROLE OF TAURINE

Other than conjugation of bile acids and the detoxification of xenobiotics via conjugation and excretion in bile, the function of taurine in mammals is not well understood. It has been known since the mid 1970s that taurine is essential for normal retinal function in cats.[89] Taurine is essential for normal myocardial function.[90–94] Despite *in vivo* and *in vitro* studies illustrating the varied and ubiquitous effects of taurine in mammals, the basis for these effects remains unknown.

TABLE 32-4
Normal Feline Plasma and Myocardial Carnitine Concentrations in Adult Cats[78]

	Plasma Carnitine*		Myocardial Carnitine* (n = adult cats 14)	
(μM/liter)	*Male (n = 9)*	*Female (n = 4)*	*(nM/mg Noncollagenous Protein)*	
Total	13.6 ± 4.3	24.8 ± 9.8	Total	3.9 ± 0.8
Free	11.1 ± 3.6	19.4 ± 7.2	Free	2.7 ± 0.6
Esterified	2.6 ± 1.6	5.4 ± 3.1	Esterified	1.2 ± 0.4

*Mean ± standard deviation.

TAURINE PHYSIOLOGY AND METABOLISM IN THE CAT

Low tissue concentration of cysteine–sulfinic acid decarboxylase (CSAD), a key enzyme in the biosynthesis of taurine,[95] has been reported as the reason cats have a limited ability to synthesize taurine from cysteine and methionine. However, this limited synthetic ability is not unique to the cat (e.g., humans also have limited synthetic ability), and it is unlikely that this alone is sufficient to explain the cat's propensity for developing low plasma taurine concentrations and associated abnormalities.

Many mammals preferentially utilize taurine for bile acid conjugation, forming taurocholic acid; however if taurine is in low supply, glycine can be utilized so that the major bile acid produced will be glycocholate (the glycine conjugate). Cats are unable to conjugate significant amounts of their bile acids with glycine.[96] They utilize taurine exclusively for bile acid conjugation, even when dietary taurine is restricted. Continued biliary taurine loss, combined with a low synthetic ability, predisposes the cat to becoming taurine-depleted.

As an obligate carnivore, the feral cat has little risk of developing taurine deficiency. However, pet cats have been put at risk of becoming taurine-deficient through (1) the modern practice of feeding commercially produced cat foods, many of which are based upon plant products, and (2) our incomplete understanding of feline nutrition. Several significant clinical states may result from taurine deficiency, including retinal degeneration, dilated cardiomyopathy, and infertility.

TAURINE PHYSIOLOGY AND METABOLISM IN THE DOG

Taurine is not an essential amino acid in the dog. Normal dogs fed diets with little or no taurine maintain plasma and whole blood taurine concentration similar to that found in the normal cat.[97] The activity of cysteine–sulfinic acid decarboxylase (the rate-limiting enzyme in the synthesis of taurine) is high in the dog when compared with the cat.[98] However, activity of this enzyme alone does not fully explain the difference in the requirement between these two species. Dogs also conjugate bile acids solely with taurine.[99] Species differences in the balance between taurine synthesis and biliary taurine loss during bile acid conjugation qualitatively explains the dietary need for taurine in the cat and the lack of a dietary requirement in healthy dogs and humans.

Recent evidence suggests that taurine deficiency should be considered when formulating a differential diagnosis for canine DCM.[97, 100, 101]

TAURINE AND THE HEART

There is extensive literature relating taurine to physiologic, biochemical, and cellular phenomena with respect to modulation of myocardial and cardiac function. Taurine has beneficial effects in rabbits[91] and humans[92] with valvular heart disease. The identification of taurine deficiency–induced myocardial failure in pet cats, and its reversal after taurine administration,[94] is the first direct evidence that taurine deficiency can cause a clinically significant decrement in myocardial mechanical function *in vivo.*

MECHANISMS OF TAURINE DEFICIENCY

Mechanisms proposed to explain the action of taurine upon the myocardium include (1) osmoregulation (taurine is a small, highly charged, osmotically active molecule, and cellular osmoregulation induced by changes in intracellular taurine concentration may be an important mechanism in nervous tissue and myocardium[82]); (2) calcium modulation (modulation of tissue calcium concentrations and availability[90]); (3) free radical inactivation;[82] and (4) other potential mechanisms (*N*-methylation of cell membrane phospholipids;[102] direct effects upon the contractile proteins;[103, 104] and interactions with the renin-angiotensin-aldosterone system[105]).

The relationship between taurine deficiency and myocardial failure as documented in pet cats[91, 106] has heightened clinical focus on this relationship in other

species. Similar associations have been reported in foxes[107] and dogs,[100, 101] and implications for humans with DCM has been discussed.[108]

TAURINE DEFICIENCY–INDUCED MYOCARDIAL FAILURE IN CATS

EPIDEMIOLOGY

An association between DCM in pet cats, low plasma taurine concentration, and diet was reported in 1987.[94] This phenomenon has been reproduced in experimental animals[84] and was independently confirmed in a multicenter clinical study.[106] However, dilated (congestive) cardiomyopathy was widely recognized in cats by the early 1970s.[109–112] Clinical and pathologic findings had been described, and response to therapy was uniformly poor.[110, 112–114] Therefore, much of the literature referring to idiopathic DCM in cats is suspected to be really associated with taurine deficiency, representing a nutritional form of secondary cardiomyopathy.

Not all taurine-deficient cats develop myocardial failure. In repeated studies performed at the University of California at Davis, approximately 25 percent of all (n > 100) cats experimentally depleted of taurine for more than 2 years developed overt myocardial failure. Other factor(s) required for taurine deficiency–induced overt myocardial failure are unknown. A genetic predisposition has been proposed.[115] Nutritional taurine deficiency combined with other causes of myocardial "stress" (e.g., congenital or acquired left ventricular volume overload or toxic, ischemic, nutritional, endocrine, or metabolic problems) may cause complicating effects.

DIAGNOSIS

Taurine deficiency–induced myocardial failure should be suspected when (1) myocardial (i.e., systolic) failure is found concurrent with low plasma, whole blood, or tissue taurine concentrations (Table 32–5), or (2) when other systemic evidence of taurine deficiency (e.g., central retinal degeneration) is present.

Confirmation of taurine deficiency requires documenting normalization of myocardial function by serial echocardiograms after taurine supplementation. No criterion conclusively differentiates between taurine deficiency–induced myocardial failure and primary idiopathic DCM. Lack of echo and clinical response to taurine suggest idiopathic DCM (chapter 28).

HISTORY. Diet history should be ascertained to discern homemade diets containing inadequate taurine. Owners need to be educated to prevent recurrence. Occasionally, taurine deficiency DCM still occurs in cats fed commercial diets containing inadequate amounts of taurine.

TABLE 32–5
Normal Values for Feline and Canine Taurine Concentrations

Feline	
Plasma*	
Normal, > 60	
At risk, < 30 nmol/ml	
Whole blood†	
Normal, > 200 nmol/ml	
At risk, < 100 nmol/ml	
Canine[97]	
Plasma	
Normal, > 25 nmol/ml:	
	91 ± 30 nmol/ml (using lithium heparin anticoagulant)
	64 ± 16 nmol/ml (using sodium heparin anticoagulant)

*Plasma taurine concentration is VERY labile; 24 hours of fasting can cause plasma concentrations to fall below 30 nmol/ml.
†Whole blood taurine concentration is not as labile as that of plasma concentration. Fasting does not significantly affect values.

CLINICAL FINDINGS. Historical complaints, signalment, and physical examination have many similarities to other feline myocardial diseases[119] (chapter 28). Central retinal degeneration coupled with evidence of heart disease increases suspicion of taurine deficiency, although taurine deficiency–induced retinal lesions are permanent, indicating only that taurine deficiency occurred at some time. Not all taurine-deficient cats develop central retinal degeneration.

ELECTROCARDIOGRAPHY AND RADIOGRAPHY. These cannot definitively discriminate between taurine deficiency–induced myocardial failure and other forms of feline cardiac disease. Echocardiography will detect myocardial failure and cardiac chamber dilation but cannot confirm the underlying cause.

BLOOD TAURINE CONCENTRATION ASSAY. Cats with any form of myocardial failure should have blood drawn for plasma and whole blood taurine concentration assays before taurine administration (Table 32–6). Oral

TABLE 32–6
Guidelines for Processing Blood Samples for Taurine Analysis

Draw samples for both heparinized plasma and heparinized whole blood*
Place sample on wet ice, or centrifuge the sample and separate plasma immediately
Make sure the sample contains no clots or hemolysis
Store and ship samples frozen (dry ice or ice packs)

*Whole blood analysis is most accurate.

taurine is rapidly concentrated in the heart.[85] Even a single dose will make interpretation difficult.

THERAPY

When myocardial failure is detected or clinically suspected in cats, the following guidelines are suggested.

1. If CHF is present, supportive and symptomatic care is essential during initial therapy (chapters 12, 28). Digoxin is not essential, nor is it contraindicated.
2. Cats with documented or suspected taurine deficiency should have supplemental taurine, 250 mg orally every 12 hours until echocardiographic left ventricular dimensions and contractility normalize. This usually occurs within 4 months in cases of taurine deficiency DCM. Clinical improvement is usually evident within about 2 weeks.
3. Diuretics and ACE inhibitors can be discontinued when signs of CHF resolve. While withdrawing medications, the respiratory rate must be monitored and prompt re-evaluation scheduled if tachypnea, dyspnea, or anorexia occur.
4. Clinical examination, including radiographic or echocardiographic evaluation, should be repeated 1 week after withdrawing medications.
5. The diet should be altered to maintain normal plasma taurine concentrations (> 60 nmol/ml) or normal whole blood taurine concentration (> 200 nmol/ml).
6. Taurine supplementation can be discontinued once echocardiographic values normalize as long as diet modification maintains a normal plasma taurine concentration.
7. Taurine concentration should be monitored periodically to assure that the diet is maintaining acceptable blood taurine levels. If taurine concentrations became depleted again, many cats will redevelop myocardial failure.

PROGNOSIS

All cats with myocardial failure should immediately have supplemental taurine. The initial prognosis is guarded to grave. Approximately one third of affected cats die within the first week after diagnosis. Hypothermia and thromboembolism confer a poor prognosis. Taurine supplementation does not provide survival benefit until 2 weeks after treatment is begun. The prognosis can be upgraded to fair for cats that survive 1 week and respond to CHF therapy. Cats that survive 2 weeks have a good prognosis.

Most taurine-responsive cats have complete resolution of echocardiographic and clinical abnormalities after taurine supplementation.[106, 119] Occasionally, residual mild myocardial failure (left ventricular shortening fraction 25 to 30 percent) is recorded, although these cats are generally asymptomatic and rarely require therapy other than maintaining normal plasma taurine concentrations.

PREVENTION OF FELINE TAURINE DEFICIENCY

As taurine deficiency is believed to result from inadequate dietary taurine, it is preventable in most cases. A precise requirement for taurine cannot be determined for all foods because the requirement depends upon many factors.[94, 116–118] No commercial diet should be assumed to be taurine sufficient unless the manufacturer has provided feeding trial data documenting that it maintains normal blood and tissue taurine concentrations while feeding for at least 6 months. Since the late 1980s, manufacturers of commercial diets have supplemented cat foods with additional taurine, which has greatly reduced the prevalence of feline DCM (chapter 28).[118a]

TAURINE DEFICIENCY AND MYOCARDIAL FAILURE IN DOGS

Unlike cats, dogs are much less prone to plasma taurine deficiency. Few studies evaluating taurine and canine heart disease have been reported.

EPIDEMIOLOGY

In the largest study of plasma taurine and canine heart disease, 71 dogs with DCM and 32 with chronic acquired valvular disease were evaluated.[97] Plasma taurine concentration was low (< 20 nmol/ml) in 12 dogs with DCM but was normal or high in dogs with chronic acquired valvular disease. Breeds representing these 12 affected dogs were generally not representative of breeds commonly associated with DCM. Only one dog had a history of an abnormal (vegetarian) diet and improved clinically following taurine supplementation. The cause of low plasma taurine in the other dogs, and whether it was associated with generalized tissue taurine depletion, was not reported.

The relationship of taurine and myocardial failure is being evaluated in other breeds. American cocker spaniels with DCM were responsive to taurine and L-carnitine supplementation.[100, 101] Plasma taurine concentrations at baseline were low (< 50 nM/ml). Plasma taurine concentration did increase during taurine supplementation. Plasma carnitine concentrations were within, only slightly below, or above reported normal limits at baseline; they did not change during placebo administration and increased during supplementation. The cause of decreased plasma taurine concentration in these dogs is unknown.

THERAPY

In American cocker spaniels with DCM, echocardiographic left ventricular dimensions did not change during placebo administration but did improve during supplementation with taurine and carnitine. The shortening fraction increased significantly but not into the normal range. Echocardiographic variables remained improved at 6 months. Thus, some American cocker spaniels with DCM may be taurine deficient and responsive to taurine and carnitine supplementation. Central retinal degeneration was observed in two cocker spaniels with low plasma taurine concentration and DCM, suggesting that generalized tissue taurine depletion was present in these cases.[100, 101]

The relative role of carnitine and taurine in the pathogenesis of canine DCM deserves greater study.

CARDIOVASCULAR DISEASE AND OTHER NUTRITIONAL CONSIDERATIONS

Relationships between cardiovascular disease and other nutritional abnormalities represent areas of increasing investigation. A number of nutritional disturbances have been associated with systemic and cardiovascular manifestations in animals, including atherosclerosis,[120] obesity,[121] and deficiencies in selenium and vitamin E,[122] B vitamins,[123] and thiamine.[124]

Epidemiologic relations were evaluated between plasma concentrations of nutrients and feline cardiovascular diseases in 220 cats.[125] A number of significant differences were recorded in plasma concentrations of α-tocopherol, retinol, total triglycerides, and cholesterol among cats with hyperthyroidism and hypertrophic and dilated cardiomyopathies. The clinical importance, if any, of these abnormalities remains to be elucidated. Elevated plasma homocysteine concentration has been linked to a wide variety of vascular diseases.[126] Some cats with cardiomyopathy and arterial thromboembolism have homocysteinemia (Hohenhaus AE, et al. Unpublished data, 1998).

REFERENCES

1. Hamlin RL, Buffington CAT. Nutrition and the heart. Vet Clin North Am Small Anim Pract 19:527, 1989
2. Ross JN. Heart failure. *In* Lewis LD, Morris ML, Hand MS (eds): Small Animal Clinical Nutrition III. 3rd ed. Topeka, KS, Mark Morris Associates, 1987, p 11.1
3. Pensinger RR. Dietary control of sodium intake in spontaneous congestive heart failure in dogs. VM/SAC 59:752; 784, 1964
4. Morris ML, Patton RL, Teeter SM. Low sodium diet in heart disease: How low is low? VM/SAC 71:1225, 1976
5. Leaf A. The clinical and physiologic significance of the serum sodium concentration. N Engl J Med 267:24, 1962
6. Spann JF, Hurst JW. The recognition and management of heart failure. *In* Hurst JW (ed): The Heart, Arteries and Veins. 7th ed. New York, McGraw-Hill, 1990, p 418
7. Bonagura JD, Lehmkuhl LB. Fluid and diuretic therapy in heart failure. *In* DiBartola SP (ed): Fluid Therapy in Small Animal Practice. Philadelphia, WB Saunders, 1992, p 529
8. Oh MS, Carrol HJ. Disorders of sodium metabolism: Hypernatremia and hyponatremia. Crit Care Med 20:94, 1992
9. Packer M, Medina N, Yushak M. Correction of dilutional hyponatremia in severe chronic heart failure by converting-enzyme inhibition. Ann Intern Med 100:782, 1984
10. Rose BD. Clinical Physiology of Acid-Base and Electrolyte Disorders. 3rd ed. New York, McGraw-Hill, 1989, p 617
11. Nicod P, Biollax J, Waeber B, et al. Hormonal, global, and regional haemodynamic responses to a vascular antagonist of vasopressin in patients with congestive heart failure with and without hyponatremia. Br Heart J 56:433, 1986
12. Ware WA, Lund DD, Subieta AR, Schmid PG. Sympathetic activation in dogs with congestive heart failure caused by chronic mitral valve disease and dilated cardiomyopathy. J Am Vet Med Assoc 197:1475, 1990
13. Fray JCS, Johnson MD, Barger AC. Renin release and pressor response to renal arterial hypotension: Effect of dietary sodium. Am J Physiol 233:H191, 1977
14. Stephens GA, Davis JO, Freeman RH, et al. Hemodynamic, fluid, and electrolyte changes during sodium depletion in conscious dogs. Proc Soc Exp Biol Med 163:416, 1980
15. Rocchini AP, Cant JR, Barger AC. Carotid sinus reflex in dogs with low- to high-sodium intake. Am J Physiol 322:H196, 1977
16. Hamlin RL, Smith RC, Smith CR, Powers TE. Effects of a controlled electrolyte diet, low in sodium, on healthy dogs. VM/SAC 59:748, 1964
17. Cowgill LD, Kallett AJ. Systemic hypertension. *In* Kirk RW (ed): Current Veterinary Therapy IX: Small Animal Practice. Philadelphia, WB Saunders, 1986, p 360
18. Watkins L, Burton JA, Haber E, et al. The renin-angiotensin-aldosterone system in congestive heart failure in conscious dogs. J Clin Invest 57:1606, 1986
19. Hamlin RL, Smith CR, Ross JN. Detection and quantification of subclinical heart failure in dogs. J Am Vet Med Assoc 150:1513, 1967
20. Ettinger SJ. Valvular heart disease. *In* Ettinger SJ (ed): Textbook of Veterinary Internal Medicine. Philadelphia, WB Saunders, 1989, p 1031
21. Keene BW, Rush JE. Therapy of heart failure. *In* Ettinger SJ (ed): Textbook of Veterinary Internal Medicine. Philadelphia, WB Saunders, 1989, p 939
22. Ralston SL, Fox PR. Dietary management, nutrition, and the heart. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 219
23. White RJ, Chamberlain DA, Hamer J, et al. Potassium depletion in severe heart disease. Br Med J 2:606, 1969
24. Cobb MA, Michell AR. Plasma electrolyte concentrations in dogs receiving diuretic therapy for cardiac failure. J Small Anim Pract 33:526, 1992

25. Roudebush P, Allen TA, Kuehn NF, et al. The effect of combined therapy with captopril, furosemide, and a sodium-restricted diet on serum electrolyte concentrations and renal function in normal dogs and dogs with congestive heart failure. J Vet Intern Med 8:337, 1994
26. White RJ, Chamberlain DA, Hamer J, et al. Potassium depletion in severe heart disease. Br Med J 2:606, 1969
26a. Roudebush P. Strategies for avoiding diet-drug interactions in dogs with cardiac disease and failure. Vet Med 89(Suppl):714, 1994
27. Kelly RA. Cardiac glycosides and congestive heart failure. Am J Cardiol 65:10E, 1990
28. Woosley RL. Pharmacokinetics and pharmacodynamics of antiarrhythmic agents in patients with congestive heart failure. Am Heart J 114:1280, 1987
29. Chakko SC, Frutchey J, Gheorghiade M. Life-threatening hyperkalemia in severe heart failure. Am Heart J 117:1083, 1989
29a. The COVE Study Group. Controlled clinical evaluation of enalapril in dogs with heart failure: Results of the Cooperative Veterinary Enalapril Study Group. J Vet Intern Med 9:243, 1995
29b. Khanna C, Lund EM, Raffe M, et al. Hypomagnesemia in 188 dogs: A hospital population-based prevalence study. J Vet Intern Med 12:304, 1998
29c. Boiko R, Plasma-magnesiumkonzentration bei Hunden mit Dilatativer Kardiomyopathie und/oder Atrioventrikularklappenfibrose. Doktors der Veterinärmedizin an der Freien Universität Berlin, 1996
30. Gottlieb SS, Baruch L, Kukin ML. Prognostic importance of the serum magnesium concentration in patients with congestive heart failure. J Am Coll Cardiol 16:827, 1990
31. Ralston MA, Murnane MR, Unverferth DV, Leier CV. Serum and tissue magnesium concentrations in patients with heart failure and serious ventricular arrhythmias. Ann Intern Med 113:841, 1990
31a. Haigney MC, Kaab WS, Griffiths E, et al. Loss of cardiac magnesium in experimental heart failure prolongs and destabilizes repolarization in dogs. J Am Coll Cardiol 31:701, 1998
32. Dyckner T, Wester PO, Widman L. Amiloride prevents thiazide-induced intracellular potassium and magnesium losses. Acta Med Scand 224:25, 1988
33. Gottlieb SS. Importance of magnesium in congestive heart failure. Am J Cardiol 631989:39G, 1989
34. Reinhart RA. Magnesium metabolism. A review with special reference to the relationship between intracellular content and serum levels. Arch Intern Med 148:2415, 1988
35. Dorup I, Skajaa K, Clausen T, Kjeldsen K. Reduced concentrations of potassium magnesium and sodium pumps in human skeletal muscle during treatment with diuretics. Br Med J 296:455, 1988
36. Edwards NJ. Magnesium and congestive heart failure; Abstract. Proceedings, 9th Annual ACVIM Forum 1:679, 1991
37. Withering W. An account of the Foxglove and some of its medicinal uses. Birmingham, Swinney, 1785
38. Carr JG, Stevenson LW, Walden JA, Heber D. Prevalence and hemodynamic correlates of malnutrition in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 63:709, 1989
38a. Schwengel RH, Gottlieb SS, Fisher ML. Protein-energy malnutrition in patients with ischemic and nonischemic dilated cardiomyopathy and congestive heart failure. Am J Cardiol 73:908, 1994
39. Pittman JG, Cohen P. The pathogenesis of cardiac cachexia. N Engl J Med 271:403, 1964
40. Ansari A. Syndromes of cardiac cachexia and the cachectic heart: Current perspective. Prog Cardiovasc Dis 30:45, 1987
41. Harrison JV. Diet therapy in congestive heart failure; Abstract. J Am Dietet Assoc 21:86, 1945
42. Bologna A, Costadoni A. Osservazioni sulla funzonione gastropancreatica nei cardiopazienti. Arch ital mal l'app digest 7:215, 1938
43. Berkowitz D, Croll MN, Likoff W. Malabsorption as a complication of congestive heart failure. Am J Cardiol 11:43, 1963
44. Strober W, Cohen LS, Waldmann TA, Braunwald E. Tricuspid regurgitation: A newly recognized cause of protein-losing enteropathy, lymphocytopenia and immunologic deficiency. Am J Med 44:842, 1968
45. Peterson VP, Hastrup J. Protein-losing enteropathy in chronic constrictive pericarditis; Abstract. Acta Med Scand 173:401, 1963
46. Miller MW, Bonagura JD, DiBartola SP, Fossum TW. Budd-Chiari-like syndrome in two dogs. J Am Anim Hosp Assoc 25:277, 1989
47. Cohn AE, Steele JM. Unexplained fever in heart failure. J Clin Invest 13:853, 1934
48. McIlroy MB. Dyspnea and the work of breathing in diseases of the heart and lungs. Progr Cardiovasc Dis 1:284, 1959
49. Olson RE. Myocardial metabolism in congestive heart failure. J Chronic Dis 9:442, 1959
50. Knowlen GG, Kittleson MD, Nachreiner RF, Eyster GE. Comparison of plasma aldosterone concentration among clinical status groups of dogs with chronic heart failure. J Am Vet Med Assoc 183:991, 1983
51. Csky TZ, Hetzog HJ, Fernald JW. Effects of digitalis on active intestinal sugar transport. Am J Physiol 200:459, 1961
52. Oliff A. The role of tumor necrosis factor (cachetin) in cachexia. Cell 54:141, 1988
52a. Anker SD, Clark AL, Kemp M, et al. Tumor necrosis factor and steroid metabolism in chronic heart failure: Possible relation to muscle wasting. J Am Coll Cardiol 30:997, 1997
53. Levine B, Kalman J, Mayer L, et al. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 323:236, 1990
54. McMurray J, Abdullah I, Dargie HJ, Shapiro D. Increased concentrations of tumour necrosis factor in "cachectic" patients with severe chronic heart failure. Br Heart J 66:356, 1991
55. Freeman LM, Rush JE, Brown DJ, Roubenoff R. Elevated concentration of tumor necrosis factor in dogs with congestive heart failure; Abstract. J Vet Intern Med 8:146, 1994
55a. Meurs KM, Miller MW, Fox PR, et al. Serum tumor necrosis factor concentration in cats with congestive heart failure; Abstract. J Vet Internal Med 9:200, 1995
56. Dzau VJ, Packer M, Lilly LS, et al. Prostaglandins in severe congestive heart failure: Relation to activation of the renin-angiotensin system and hyponatremia. N Engl J Med 310:347, 1984
57. Renz H, Gong JH, Nain M, Gemsa D. Release of tumor necrosis factor from macrophages: Enhancement and suppression are dose dependently regulated by prostaglandin E_2 and cyclic nucleotides. J Immunol 141:2388, 1988
58. Endres S, Ghorbani R, Kelley VE, et al. The effect of dietary supplementation with $n-3$ polyunsaturated

fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Engl J Med 320:265, 1989
59. Ross LA, Labato MA. Use of drugs to control hypertension in renal failure. *In* Kirk RW (ed): Current Veterinary Therapy X: Small Animal Practice. Philadelphia, WB Saunders, 1989, p 1201
60. Stamler R, Stamler J, Grimm R. Nutritional therapy for high blood pressure: Final report of a four-year randomized controlled trial, the Hypertension Control Program. JAMA 257:1484, 1987
61. Knapp H, FitzGerald GA. The antihypertensive effects of fish oil: A controlled study of polyunsaturated fatty acid supplements in essential hypertension. N Engl J Med 320:1037, 1989
62. Bonaa KH, Bjerve KS, Straume B. Effect of eicosapentaenoic and docosahexaenoic acids on blood pressure in hypertension. N Engl J Med 322:795, 1990
62a. Ascherio A, Rimm EB, Stampfer MJ, et al. Dietary intake of $n-3$ fatty acids, fish intake, and risk of coronary disease among men. N Engl J Med 332:977, 1995
63. Cinotti GA, Pugliese F. Prostaglandins and hypertension. Am J Hypertens 2:10S, 1989
64. McMillan DE. Antihypertensive effects of fish oil. N Engl J Med 321:1610, 1989
65. Hamazaki T, Nakazawa R, Tateno S. Effects of fish oil rich in eicosapentaenoic acid on serum lipid in hyperlipidemic hemodialysis patients. Kidney Int 26:81, 1984
66. Brown SA. Role of dietary lipids in renal disease in the dog; Abstract; Proceedings, 10th Annual ACVIM Forum, 1992, p 568
67. Bremer J. Carnitine—metabolism and functions. Physiolog Rev 63:1420, 1983
68. Roe CR, Millington DS, Malthy DA, et al. L-Carnitine enhances excretion of propionyl coenzyme A as propionyl carnitine in propionic acidemia. J Clin Invest 73:1785, 1984
69. Engel AG, Angelini C. Carnitine deficiency of human skeletal muscle associated with lipid storage myopathy: A new syndrome. Science 179:899, 1973
70. Tripp ME, Katcher ML, Peters HA, et al. Systemic carnitine deficiency presenting as familial endocardial fibroelastosis: A treatable cardiomyopathy. N Engl J Med 305:385, 1981
71. Keene BW, Panciera DP, Atkins CE, et al. Myocardial L-carnitine deficiency in a family of dogs with dilated cardiomyopathy. J Am Vet Med Assoc 198:647, 1991
72. Rebouche CJ, Engel AG. Kinetic compartmental analysis of carnitine metabolism in the dog. Arch Biochem Biophys 220:60, 1983
73. Winter SC. Plasma carnitine deficiency: Clinical observations in 51 pediatric patients. Am J Dis Child 141:660, 1987
74. Keene BW, Kittleson ME, Atkins CE, et al. Modified transvenous endomyocardial biopsy technique in dogs. Am J Vet Res 51:1769, 1990
75. Parvin R, Pande SV. Microdetermination of carnitine and acetylcarnitine transferase activity. Anal Biochem 79:190, 1977
76. Pierpont ME, et al. Myocardial carnitine metabolism in congestive heart failure induced by incessant tachycardia. Basic Res Cardiol 88:362, 1993
77. Treem WR, Stanley CA, Finegold DN, et al. Primary carnitine deficiency due to a failure of carnitine transport in kidney, muscle, and fibroblasts. N Engl J Med 319:1331, 1988
78. Jacobs G, Keene B, Cornelius LM, et al. Plasma, tissue and urine carnitine concentrations in healthy adult cats and kittens. Am J Vet Res 51:1345, 1990
78a. Fox PR. Unpublished data, 1992
79. Keene BW, Kittleson MD, Rush JE, et al. Myocardial carnitine deficiency associated with dilated cardiomyopathy in Doberman pinschers; Abstract. Proceedings of the ACVIM, 1989
80. Mancini M, Rengo F, Lingetti M, et al. Controlled study on the therapeutic efficacy of propionyl-L-carnitine in patients with congestive heart failure. Arzneimittelforschung 42:1101, 1992
81. Kobayashi A, Masumura Y, Yamazaki N. L-Carnitine treatment for congestive heart failure—experimental and clinical study. Jpn Circ J 56:86, 1992
82. Huxtable RJ. Physiological actions of taurine. Physiolog Rev 72:101, 1992
83. Sturman JA, Gargano AD, Messing JM, Imaki H. Feline maternal taurine deficiency: Effect on mother and offspring. J Nutr 116:655, 1986
84. Pion PD, Kittleson MD, Skiles ML, et al. Dilated cardiomyopathy associated with taurine deficiency in the domestic cat: Relationship to diet and myocardial taurine content. Adv Exp Med Biol 315:63, 1992
85. Fox PR, Sturman JA. Myocardial taurine concentrations in cats with cardiac disease and in healthy cats fed taurine-modified diets. Am J Vet Res 53:237, 1992
86. Pion PD, Lewis J, Greene K, et al. Effect of meal-feeding and food deprivation on plasma and whole blood taurine concentrations in cats. J Nutr 121(11 Suppl):S177, 1991
87. Schuller-Levis G, Mehta PD, Rudelli R, Sturman J. Immunologic consequences of taurine deficiency in cats. J Leukocyte Biol 47:321, 1990
88. Huxtable RJ, Chubb J, Azari J. Physiological and experimental regulation of taurine content in the heart. Fed Proc 39:2685, 1980
89. Hayes KC, Carey RE, Schmidt SY. Retinal degeneration associated with taurine deficiency in the cat. Science 188:949, 1975
90. Huxtable RJ. From heart to hypothesis: A mechanism for the calcium modulatory actions of taurine. Adv Exp Med Biol 217:371, 1987
91. Takihara K, Azuma J, Awata N, et al. Beneficial effect of taurine in rabbits with chronic congestive heart failure. Am Heart J 112:1278, 1986
92. Azuma J, Sawamura A, Awata N, et al. Therapeutic effect of taurine in congestive heart failure: A double-blind crossover trial. Clin Cardiol 8:276, 1985
93. Schaffer SW, Seyed-Mozaffari M, Kramer J, Tan BH. Effect of taurine depletion and treatment on cardiac contractility and metabolism. Prog Clin Biol Res 179:167, 1985
94. Pion PD, Kittleson MD, Rogers QR, Morris JG. Myocardial failure in cats associated with low plasma taurine: A reversible cardiomyopathy. Science 237:764, 1987
95. Morris JH, Rogers QR. The metabolic basis for the taurine requirement of cats. Adv Exp Med Biol 315:33, 1992
96. Rabin B, Nicolosi RJ, Hayes KC. Dietary influences on bile acid conjugation in the cat. J Nutr 106:1241, 1976
97. Kramer GA, Kittleson MD, Fox PR, et al. Plasma taurine concentration in normal dogs and in dogs with heart disease. J Vet Intern Med 9:253, 1995
98. Jacobsen JG, Thomas LL, Smith LH Jr. Properties and distribution of mammalian L-cysteine sulfinate carboxylases. Biochem Biophys Acta 85:103, 1964
99. Haslewood GAD. The biological significance of chemical differences in bile salts. Biol Rev 39:537, 1964
100. Kittleson MD, Pion PD, DeLellis LA, Tobias AH. Dilated cardiomyopathy in American cocker spaniels—taurine

deficiency and preliminary results of response to supplementation. New Orleans, ACVIM Scientific Proceedings, 1991
101. Kittleson MD, Keene B, Pion PD, et al. Results of the Multicenter Spaniel Trial (MUST): Taurine and carnitine responsive dilated cardiomyopathy in American cocker spaniels with decreased plasma taurine concentrations. J Vet Intern Med 11:204, 1997
102. Hamaguchi T, Azuma J, Schaffer S. Interaction of taurine with methionine: Inhibition of myocardial phospholipid methyltransferase. J Cardiovasc Pharm 18:224, 1991
103. Lake N. Loss of cardiac myofibrils: Mechanism of contractile deficits induced by taurine deficiency. Am J Physiol 264:H1323, 1993
104. Steele DS, Smith GL, Miller DJ. The effects of taurine on Ca2+ uptake by the sarcoplasmic reticulum and Ca2+ sensitivity of chemically skinned rat heart. J Physiol 422:499, 1990
105. Gentile S, Bologna E, Terracina D, Angelico M. Taurine-induced diuresis and natriuresis in cirrhotic patients with ascites. Life Sci 54:1585, 1994
106. Sisson DD, Knight KH, Helinski C, et al. Plasma taurine concentrations and M-mode echocardiographic measures in healthy cats and in cats with dilated cardiomyopathy. J Vet Intern Med 5:232, 1991
107. Moïse NS, Pacioretty LM, Kallfelz FA, et al. Dietary taurine deficiency and dilated cardiomyopathy in the fox. Am Heart J 121:541, 1991
108. Tenaglia A, Cody R. Evidence for a taurine-deficiency cardiomyopathy. Am J Cardiol 62:136, 1988
109. Liu S-K. Congestive heart failure in the cat. J Am Vet Med Assoc 156:1319, 1970
110. Harpster NK. Acquired heart disease in the cat. Proceedings, 40th Annual Meeting, American Animal Hospital Association; 1973, p 118
111. Liu SK. Pathology of feline heart disease. Vet Clin North Am 7:323, 1977
112. Liu SK, Tilley LP. Animal models of myocardial diseases. Yale J Biol Med 53:191, 1980
113. Van Vleet JF, Ferrans VJ, Weirich WE. Pathologic alterations in hypertrophic and congestive cardiomyopathy of cats. Am J Vet Res 41:2037, 1980
114. Lord PF, Wood A, Tilley LP, Liu SK. Radiographic and hemodynamic evaluation of cardiomyopathy and thromboembolism in the cat. J Am Vet Med Assoc 164:154, 1974
115. Lawler DF, Templeton AJ, Monti KL: Evidence for genetic involvement in feline dilated cardiomyopathy. J Vet Intern Med 7:383, 1993
116. Hickman MA, Bruss ML, Morris JG, Rogers QR. Dietary protein source (soybean vs. casein) and taurine status affect kinetics of the enterohepatic circulation of taurocholic acid in cats. J Nutr 122:1019, 1992
117. Hickman MA, Rogers QR, Morris JG. Taurine balance is different in cats fed purified and commercial diets. J Nutr 122:553, 1992
118. Hickman MA, Rogers QR, Morris JG. Effect of processing on fate of dietary [14C]taurine in cats. J Nutr 120:995, 1990
118a. Fox PR. Feline myocardial diseases. 18th Annual Waltham/OSU Symposium. Cardiology. Vernon, CA, Waltham USA, 1994, p 119
119. Pion PD, Kittleson MD, Thomas WP, et al. Clinical findings in cats with dilated cardiomyopathy and relationship of findings to taurine deficiency. J Am Vet Med Assoc 201:267, 1992
120. Zhu BQ, Parmley WW. Modification of experimental and clinical atherosclerosis by dietary fish oil. Am Heart J 119:168, 1990
121. Messerli FH. Cardiomyopathy of obesity—a not-so-Victorian disease. N Engl J Med 314:378, 1986
122. Van Vleet JF. Current knowledge of selenium–vitamin E deficiency in domestic animals. J Am Vet Med Assoc 176:321, 1980
123. Steier M, Lopez R, Cooperman JM. Riboflavin deficiency in infants and children with heart disease. Am Heart J 92:139, 1976
124. Kawai C, Wakabayashi A, Matsumara T, et al. Reappearance of beriberi heart disease in Japan: A study of 23 cases. Am J Med 69:383, 1980
125. Fox PR, Trautwein EA, Hayes KC, et al. Comparison of taurine, α-tocopherol, retinol, selenium, and total triglycerides and cholesterol concentrations in cats with cardiac disease and in healthy cats. Am J Vet Res 54:563, 1993
126. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med 338:1042, 1998

33

Cardiac Manifestations of Systemic and Metabolic Disease

CLARKE E. ATKINS

The effects of many systemic and metabolic diseases on cardiac structure and function are well recognized. In some cases they may constitute the major clinical concern; in others, these effects may be subtle or of minimal importance.[1] Discussion focuses upon those disorders that are most clinically important and for which adequate documentation exists. Relevant therapies are reviewed in their respective chapters.

CARDIOMYOPATHY OF OVERLOAD

Adaptive responses in the failing heart compensate for stresses imparted by sustained volume or pressure overload. One of the main causes of cardiac deterioration in these chronic settings is a type of cardiomyopathy referred to as "cardiomyopathy of overload" or "deterioration of the chronically overloaded heart."[2] This pathophysiology provides insight into important cardiac cellular alterations and affects therapeutic strategies for clinical management.

Cardiac hypertrophy is a significant compensatory mechanism that develops in response to a pressure or volume overload. It may be physiologic, be readily reversible, and lack detrimental effects. Alternatively, it may constitute a pathologic response to preload and afterload stresses (volume and pressure loading, respectively), loss of myocytes (e.g., infarct), or diminished contractility (e.g., cardiomyopathy).[3] Except in neonates in whom myocyte hyperplasia is active, increases in muscle mass result from hypertrophy (an increase in individual cell size). Initially, mitochondrial mass increases, providing increased adenosine triphosphate (ATP) for the energy demands of hypertrophy. With time, myofibrillar mass increases and ultimately outstrips mitochondrial proliferation.[3]

In the compensated state, both volume overloading and pressure overloading change ventricular geometry and wall thickness. This minimizes elevations that occur in systolic wall stress.[4] End-diastolic wall stress increases with volume but not with pressure overload states.

Volume overload states (e.g., arteriovenous fistulas) result in *eccentric hypertrophy*. This is characterized by ventricular dilatation with increased ventricular volume and mass. It is accompanied by an early rise and then mainte-

nance of end-diastolic pressure. Sarcomere length is optimized and maintained at 2.2 μm. Because new sarcomeres are laid down in series, there is no disengagement of actin and myosin myofilaments, despite progressive ventricular luminal dilatation. In the compensated state of chronic volume overload, stroke volume is enhanced because the sarcomere length is optimal, and individual myocardial unit function is nearly normal. Increased preload enhances contractility by increasing the sensitivity of myofilaments to calcium.[5] With time and large volume overload, slippage between fibrils may occur, myocardial contractility decreases, and heart failure ensues.[2, 3]

Pressure overload states (i.e., increased wall stress), such as occurs with systemic hypertension, produces eccentric and then *concentric hypertrophy*.[6] The latter results when cardiac myofibrils are laid down in parallel, which increases cross-sectional diameter and mass. Ventricular pressures increase (systolic ventricular pressure increases much more than in volume overload states). Wall stress is "normalized" with concentric hypertrophy and maintained at a near-normal level.[3] Decompensation is associated with alterations in ultrastructural organization, myofibril lysis, cell death, and fibrosis.[2, 3] If this state is severe and prolonged, myocardial "exhaustion" and failure ensue, with resultant heart failure (Fig. 33–1).

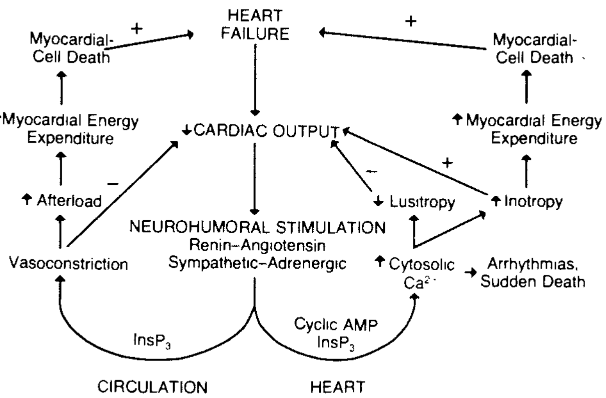


FIGURE 33–1

Cardiovascular adaptations to heart failure associated with volume or pressure loads caused by cardiac or noncardiac diseases. Ultimately, cardiac cell death and "cardiomyopathy of overload" may result (see text for details). The stimulated neurohumoral systems affect the circulation and heart. Vasoconstriction increases afterload, which further decreases cardiac output and accelerates myocardial cell death by increasing cardiac work. Increased cardiac cyclic AMP and inositol-1,4,5-tris phosphate (*InsP*$_3$) promote Ca^{++} entry, augmenting contractility; along with a chronotropic effect (not shown), this increases cardiac output. However, increased Ca^{++} entering the cytosol can overload the systems that pump this ion out of the cell during diastole, thus impairing relaxation; Ca^{++} overload may also induce arrhythmias and sudden death. Thus, when the initial adaptive responses of both the circulation and the heart to a chronic low-output state become sustained, they can have deleterious long-term effects. (Reprinted with permission from Katz AM: Cardiomyopathy of overload. N Engl J Med 322:100, 1990. Copyright 1990 Massachusetts Medical Society.)

Hypertrophy generally provides short-term benefits, whether incited by cardiac or noncardiac disease or neurohumoral responses to falling cardiac output (Table 33–1; Fig. 33–1).[2] It initially "unloads" cardiac myocytes by adding sarcomeres, which is an early, energy-sparing beneficial effect. However, these changes may alter the relationship of the myocardium to its capillaries, increasing intercapillary distances and altering oxygen perfusion. Severe hypertrophy may ultimately result in a larger heart with greater energy needs, attended by relatively fewer mitochondria that are receiving less nutrients for ATP production. Increased collagen synthesis associated with acute overloading may help maintain wall stress by preventing dilatation during early hypertrophy. However, this can eventually impair cardiac diastolic properties.[2]

Pathologic hypertrophy contributes to diastolic dysfunction by slowing the active, energy-requiring process of relaxation and by increasing diastolic stiffness.[3] Chamber stiffness can result from increased wall thickness (caused by pressure overload), increased end-diastolic volume (caused by volume overload), temporary ischemia, and fibrosis. Increased intrinsic myocardial stiffness accompanying afterload-induced hypertrophy may worsen diastolic dysfunction.[7] Prolonged relaxation may occur with ventricular hypertrophy associated with increased afterload, volume overload, temporary ischemia, and delayed inactivation of contraction. The latter is associated with diminished or slowed intracellular calcium uptake by the sarcoplasmic reticulum from subnormal intracellular ATP concentration.[2, 8]

In the failing heart, ventricular walls initially thicken but may then undergo thinning in end-stage failure. Necrotic cardiac myocytes are replaced by fibrous connective tissue. Resultant chamber dilatation increases wall tension, which further escalates cardiac energy requirements. Ultimately, with prolonged and excessive cardiac overloading, decompensation occurs ("cardiomyopathy of overload"). This results in systolic failure, diastolic dysfunction, and congestive heart failure.[2]

In addition to these mechanical changes in the failing heart, biochemical alterations occur. Cardiac muscle protein composition is altered; myosin ATPase activity is depressed; plasma and muscle carnitine concentrations (necessary for energy-providing fatty acid entry into mitochondria) are diminished; and sarcoplasmic reticulum calcium uptake is reduced, with a negative impact on diastolic function.[2, 9] Arrhythmias may occur and be associated with relative ischemia, conduction inhomogeneities resulting from hypertrophy and fibrosis, increased intracellular calcium concentration, and possibly structural changes in ion channels. Finally, autonomic abnormalities occur: increased plasma and subnormal myocardial norepi-

TABLE 33-1
Short-Term and Long-Term Responses to Impaired Cardiac Performance

Response	Short-Term Effects*	Long-Term Effects†
Salt and water retention	Augments preload	Pulmonary congestion, anasarca
Vasoconstriction	Maintains blood pressure to perfuse vital organs (brain/heart)	Exacerbates pump dysfunction (afterload mismatch); ↑ cardiac energy expenditure
Sympathetic stimulation	↑ Heart rate and ejection	↑ Energy expenditure
Sympathetic desensitization	—	Spares energy
Hypertrophy	Unloads individual muscle fibers	Cardiac cell deterioration/death; cardiomyopathy of overload
Capillary deficit	—	Leads to energy starvation
Mitochondrial density	↑ Density helps meet energy demands	↓ Density leads to energy starvation
Appearance of slow myosin	—	↑ Force, ↓ shortening velocity and contractility; energy sparing
Prolonged action potential	—	↑ Contractility, energy expenditure
↓ Density of sarcoplasmic reticulum Ca^{++} pump sites	—	Slows relaxation; may be energy sparing
↑ Collagen	May reduce dilatation	Impairs relaxation

*Short-term effects are mainly adaptive and occur after hemorrhage and in acute heart failure.
†Long-term effects are mainly deleterious and occur in chronic heart failure.
From Katz AM. Cardiomyopathy of overload. N Engl J Med 322:100, 1990. Copyright the Massachusetts Medical Society.

nephrine concentrations, as well as reduced numbers of beta-adrenergic receptors ("down regulation").[2]

In summary, certain adaptive mechanisms, including myocardial hypertrophy, provide short-term compensation in heart failure. Chronically, cardiac cellular and molecular abnormalities develop ("cardiomyopathy of overload"), which causes structural and functional derangements, clinical deterioration, and death.

CARDIOPULMONARY DISEASES

COR PULMONALE

Cor pulmonale denotes right ventricular hypertrophy associated with acute or chronic abnormalities of lung structure or function. In the chronic state, right ventricular hypertrophy and dilatation occur secondary to long-standing disease of the pulmonary parenchyma or vasculature or both. In acute cor pulmonale, right ventricular strain or overload is produced by acute pulmonary hypertension, usually following massive pulmonary embolism.[10] Right heart failure may result from either condition.

ETIOLOGIES. Chronic cor pulmonale often results from chronic obstructive pulmonary disease (COPD), bronchitis, bronchiectasis, emphysema, asthma, infiltrative pulmonary diseases, chronic recurrent pulmonary embolism, thoracic malformation, neuromuscular respiratory failure (myasthenia gravis), and upper airway collapse or obstruction.[10–13] In the dog, heartworm disease is probably the most important etiology of cor pulmonale. Acute cor pulmonale is usually caused by acute, massive pulmonary embolism in humans. In the dog and cat, it is most frequently associated with heartworm emboli.

PATHOPHYSIOLOGY. Cor pulmonale results when pulmonary vasoconstriction or obstruction increases pulmonary vascular resistance.[10] Important mechanisms are illustrated in Figure 33–2. Pulmonary vasoconstriction may result from disorders that directly or indirectly alter ventilation and reduce PaO_2. Alveolar hypoxia (PaO_2 < 60 mmHg in humans) is the most potent stimulus for pulmonary vasoconstriction (by release of vasoactive substances) and is locally mediated.[10–13] Dogs breathing 5 percent oxygen experimentally sustain increased pulmonary vascular resistance (more than 40% increase) and develop pulmonary hypertension within 2 minutes of hypoxia onset.[14]

The duration of hypoxia required to produce right ventricular hypertrophy (RVH) may be relatively short.[15] Acidosis also plays a clinically important role in increasing pulmonary vascular resistance, both alone and synergistically with hypoxia.[11] Pulmonary vasculature changes can occur quickly and worsen with chronicity. They diminish vascular luminal size, make pulmonary vessels rigid, and increase pulmonary vascular resistance. Such lesions include intimal thickening, inflammation and fibrosis, and medial hypertrophy. Reversibility of these vascular changes is variable and poorly defined, and depends on severity and duration.[10]

Pulmonary artery pressure may increase due to several mechanisms. The normal pulmonary vascular bed may accommodate increased blood flow with little pressure change. If flow alterations are severe or if recruitment of parallel vascular channels cannot be achieved, pulmonary artery pressure rises.[10] Further pulmonary artery pressure elevations may result from chronic hypoxemia and associated polycythemia, as

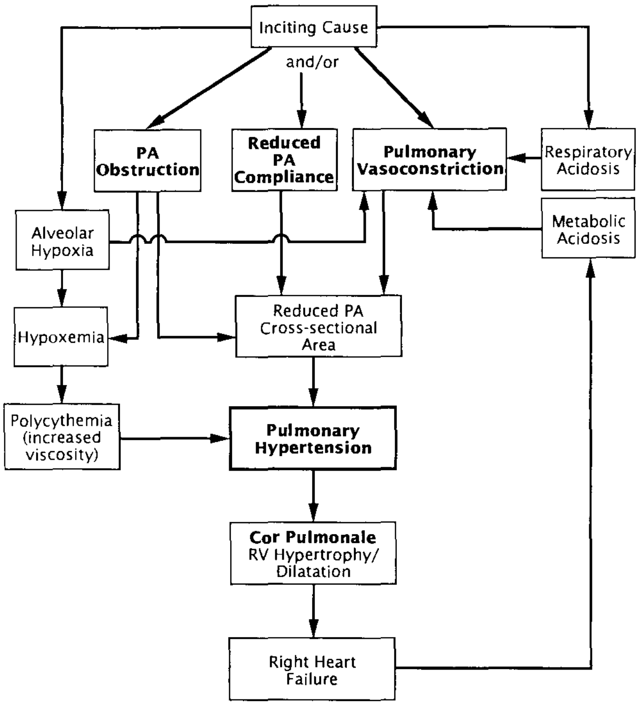


FIGURE 33–2

Pathophysiologic mechanisms important in the development of cor pulmonale and, potentially, right heart failure. See text for explanation. PA, pulmonary artery; RV, right ventricular. (Reprinted with permission from Atkins CE: The role of noncardiac disease in the development and precipitation of heart failure. Vet Clin North Am 21:1035, 1991.)

well as conditions that enhance cardiac output such as inotropic agents, volume overload, or exercise (Fig. 33–2).[10–13]

The impact on cardiac function depends on the severity and duration of increased pulmonary vascular resistance. Right ventricular oxygen consumption is increased (Fig. 33–3) and may be intermittently or permanently worsened by states of elevated cardiac output, increased blood viscosity or volume, progression or complication of underlying disease, hypoxemia, and acidosis. Early on, affected patients are essentially normal at rest. With exercise, however, they exhibit increased pulmonary artery pressure, vascular resistance, and right ventricular stroke work and reduced right ventricular ejection fraction. With severe disease, hypoxemia and moderate pulmonary hypertension occur at rest; with exercise, this worsens and is accompanied by abnormal right ventricular filling pressures and function.[10]

Falling cardiac output initiates hypertrophy and other compensatory adaptations. If severe and prolonged, pulmonary vascular disease ultimately produces "cardiomyopathy of overload"[2] with right-sided heart failure.

CLINICAL SIGNS. These depend upon the etiology of cor pulmonale and the extent of right ventricular failure. Signs of right ventricular failure may include tachycardia, hypotension, manifestations of systemic venous hypertension (e.g., jugular venous distention, hepatomegaly, ascites), murmur of tricuspid regurgitation, and a split second heart sound. Rapid, shallow breathing may result when respiratory muscles can no longer cope with excessive loads to provide effective ventilation.

THERAPY. Treatment is directed toward eliminating or palliating the underlying pulmonary hypertension. Ideally, this involves reversal of the underlying problem. Therapy might also include vasodilators, which have the potential to reduce pulmonary vascular resistance whether pulmonary hypertension is primary (idiopathic) or secondary. Reducing chronic hypoxia with oxygen therapy, improving ventilation (e.g., by re-

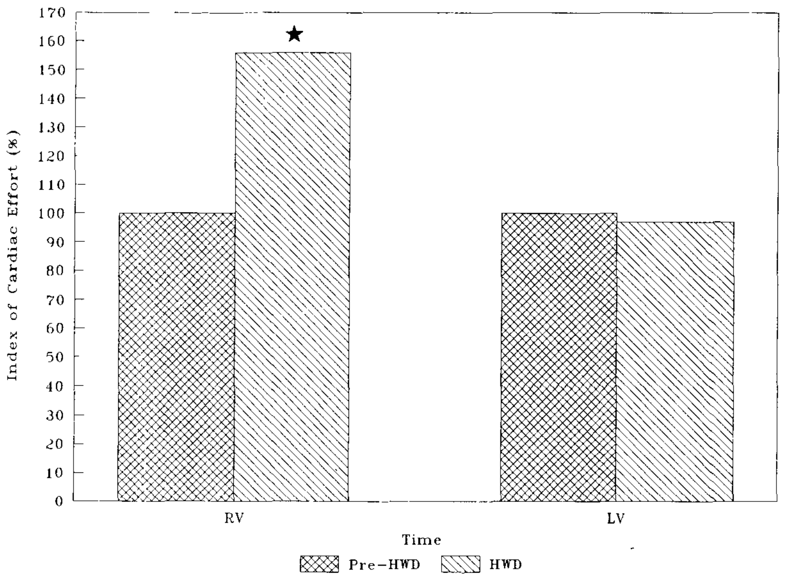


FIGURE 33–3

The effect of chronic pressure-induced hypertrophy on myocardial oxygen needs is depicted for the right and left ventricles prior to the onset, and 18 months after the onset, of heartworm disease *(HWD)*. Note that the index of cardiac effort ("double product"—product of aortic or pulmonary artery peak systolic pressure and heart rate), an indication of myocardial oxygen consumption, has increased significantly ($p < .02$) for the right ventricle *(RV)*, but not the left ventricle *(LV)*. (Reprinted with permission from Atkins CE: The role of noncardiac disease in the development and precipitation of heart failure. Vet Clin North Am 21:1035, 1991.)

versing obesity or treating a skeletal myopathy), bronchodilation, and treatment of infectious or neoplastic pulmonary infiltrative diseases may all potentially lower pulmonary vascular resistance and, hence, right ventricular afterload. Right-sided heart failure may require salt restriction, angiotensin-converting enzyme (ACE) inhibition (e.g., enalapril), and diuretics.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

While the nomenclature for COPD is somewhat controversial, it is used here to denote conditions causing largely irreversible airway obstruction. In the dog, COPD has been used to describe chronic bronchitis, bronchiectasis, emphysema, and varying degrees of airway collapse.[13–17]

PATHOPHYSIOLOGY. In canine COPD, chronic airway injury leads to chronic inflammation, excessive and viscid mucus production, increased airway resistance, and diminished expiratory flow rates. Obstruction due to mucus plugs, inflammatory exudates, and structural obliteration causes air trapping and, potentially, emphysema. Compromised pulmonary defense mechanisms allow bacterial colonization, which enhances the destructive process. Airway hyperactivity, airway collapse, and obesity represent additional adverse factors.[17] Ultimately, alveolar hypoxia results, causing pulmonary arterial vasoconstriction, increased pulmonary vascular resistance, ventilation perfusion mismatching, hypoxemia, and the potential for cor pulmonale (see Fig. 33–2). The pulmonary capillary bed cross-sectional area is decreased in severe states from pulmonary parenchymal destruction and pulmonary vessel compression (from increased intrathoracic pressure associated with air trapping).[15]

With severe COPD, the respiratory muscles function at maximal capacity to maintain ventilation. It may ultimately fail when the load becomes excessive (e.g., elastic and resistive factors increase due to lung hyperinflation and obstruction; intrinsic end-expiratory pressure also increases the inspiratory threshold load). A vicious circle may result in which worsening hypoxia, hypercapnia, and acidosis further impair respiratory muscle function. Acidosis is especially deleterious to muscle function.[17a]

CLINICAL SIGNS. Gradually progressive coughing and dyspnea with respiratory distress, expiratory wheeze, and rapid, shallow breathing occur. The electrocardiogram (ECG) often shows P pulmonale (see Figure 6–14). Acute respiratory failure is possible and must be considered in the differential diagnosis for congestive heart failure.

THERAPY. Treatment of COPD varies according to etiology but is discussed in general terms under the preceding section on cor pulmonale. Management of acute respiratory failure includes correcting life-threatening hypoxemia and acidosis, treating the underlying process, and preventing complications. In humans with acute exacerbations of COPD, noninvasive ventilation was shown to reduce the need for endotracheal intubation, the length of hospital stay, and the mortality rate. Successful therapy was accompanied by improvement in pH and a fall in the respiratory rate within the first hour of treatment.[17b]

PULMONARY THROMBOEMBOLISM

Pulmonary hypertension associated with pulmonary thromboembolism results from increased resistance to blood flow. It is present when the pulmonary artery systolic pressure is 30 mmHg or higher, the mean pulmonary artery pressure is greater than 18 mmHg, or both. Slight increases in pulmonary arterial pressure may not cause clinical or radiographic signs. But if resistance to pulmonary blood flow increases, right ventricular afterload elevates and may ultimately cause RV failure and associated signs. Affected animals may clinically improve or succumb prior to right ventricular dysfunction, especially with acute pulmonary thromboembolism.

ETIOLOGIES. Most commonly, heartworm disease (chapters 30, 31) causes pulmonary thrombosis or thromboembolism from dead worm fragments. Additional embolic causes include air, fat, sepsis, tumor, and deep venous thrombosis.[18, 19] Pulmonary thromboembolism has been associated with hypercoagulative states, vegetative endocarditis, autoimmune hemolytic anemia, protein-losing nephropathies, hyperadrenocorticism, and hypothyroidism. Long-term caging, prolonged use of indwelling venous catheters, surgical procedures, obesity, shock states, heart failure, paraneoplastic syndromes, and pregnancy are considered to be predisposing factors.[18]

PATHOPHYSIOLOGY. In dogs with pulmonary thromboembolism (PTE), pulmonary hypertension may develop after 25 to 50 percent of the pulmonary arterial cross-sectional area is occluded.[18] With significant PTE, ventilation-perfusion mismatching develops with resultant broncho- and vasoconstriction. Release of vasoactive substances from emboli further increases pulmonary vascular resistance, elevating pulmonary arterial and right ventricular pressures. Stroke volume subsequently falls; the right ventricle dilates and hypertrophies and may ultimately fail.[2] Pulmonary infarction is rare because of dual pulmonary blood supply.

Acute right ventricular pressure increases may

worsen left ventricular function by diminishing its preload, altering left ventricular distensibility, reducing left ventricular volume by ventricular septal shifting, and causing arrhythmias.[18, 19] In contrast, chronic, recurrent PTE, with partial pulmonary artery occlusion, produces more gradual increases in pulmonary vascular resistance and pulmonary arterial pressure with increased right ventricular work. Ultimately, cor pulmonale may develop.[18]

CLINICAL SIGNS. Signs may be dramatic, with acute, severe pulmonary thromboembolism. Anxiety, dyspnea, orthopnea, cough, hemoptysis, syncope, or cyanosis may occur.[18, 19] Jugular venous distention, cardiogenic shock, and occasionally ascites may be evident. Auscultation may reveal pulmonary crackles, tachycardia, split second heart sound, and murmur of tricuspid regurgitation. Radiographic findings include pleural effusion, regional oligemia, and pulmonary infiltrate representing hemorrhage, infarction, or edema.[20] Blood gas analysis typically reveals arterial hypoxemia ($PaO_2 < 80$ mmHg), metabolic acidosis, and, occasionally, respiratory acidosis.[18, 21] The ECG may show sinus tachycardia, atrial and ventricular ectopy, and evidence of right atrial and ventricular enlargement. Echocardiographic findings include septal motion abnormalities (paradoxic septal motion), enlarged right ventricular internal dimension (and RV thickening if chronic), diminished left ventricular internal dimension, and right atrial enlargement. Doppler echocardiography may disclose abnormal flow profiles of pulmonic regurgitation with high-velocity tricuspid regurgitation.

THERAPY. Treatment includes resolution of predisposing causes, O_2 therapy via nasal insufflation or O_2 cage, pulmonary vasodilation, fresh plasma in cases of antithrombin III deficiency, and antithrombotic therapy with heparin or warfarin.

ARTERIOVENOUS FISTULAS

Noncardiac arteriovenous (AV) shunts are uncommon.[22] They may be acquired (usually single) or congenital (single or multiple).

ETIOLOGY. Acquired AV fistulas can result from blunt or penetrating trauma, including iatrogenic injury,[23] or by formation of new vessels in neoplastic processes. They are located most typically in the extremities but can occur anywhere.

PATHOPHYSIOLOGY. The fistula allows blood to shunt from the high-pressure arterial to the low-pressure venous aspect of the AV connection. The resultant turbulence produces an audible, continuous bruit and often a palpable thrill. With significant shunting, volume overload will result, and a murmur of mitral insufficiency may be noted. The shunt causes regional venous blood to be hyperoxygenated, and the affected vessels proliferate, increasing the number of arteriovenous communications.[22] Vascular proliferation is accompanied by ectasia, arterial venification, and venous arterialization.[22, 24] Continuous shunting of blood produces a volume overload state, with eccentric hypertrophy and increased cardiovascular volume, afterload, and heart rate. Systolic function is typically maintained, while increased end-diastolic pressure may be adequate to produce signs of left-sided heart failure (pulmonary edema). At that point, cardiac output is typically normal to elevated.[24] Chronic volume overloading may produce cardiac decompensation with high-output heart failure (chapter 34) and, ultimately, systolic myocardial failure ("cardiomyopathy of overload").[2] Cardiac effects are related to rapidity of onset, shunt size and duration, and the presence of underlying heart disease.

CLINICAL SIGNS. The affected region may feel warm, appear swollen and painful, and have dermatologic changes such as edema, necrosis, ulceration, and pigmentation.[22, 24] A bruit and palpable thrill may be detected over the fistula. Other changes may be specific to the organ affected (e.g., ocular, central nervous system dysfunction, ascites with intrahepatic fistulas between hepatic artery and portal vein).[22] Signs of congestive heart failure may accompany long-standing or severe AV fistulas.

THERAPY. Surgical interruption or coil occlusion of the arteriovenous communication is attempted when possible. Heart failure requires standard therapy with diuretics, salt restriction, exercise restriction, vasodilators, ACE inhibitors, and digitalis.

ENDOCRINE AND METABOLIC DISORDERS

THYROID GLAND

HYPOTHYROIDISM

This is the most commonly recognized endocrinopathy in the dog, but it is rare in the cat.

ETIOLOGY. Thyroid hypofunction may be due to immune-mediated glandular destruction, or it may be idiopathic. Although it has been generally believed that hypothyroidism can complicate heart failure, there is little supportive evidence. There is anecdotal information, especially in Doberman pinschers, of isolated hypothyroidism occurring simultaneously with di-

lated cardiomyopathy.[25] Diminished myocardial function was reported in 11 hypothyroid dogs, and cardiac dysfunction was largely reversed after 2 months of levothyroxine therapy.[26]

PATHOPHYSIOLOGY. Thyroid hormone affects the heart by direct and indirect mechanisms.[27] Direct actions that increase contractility include enhanced mitochondrial protein formation and sodium-potassium ATPase activity, as well as synthesis and structural alteration of myosin. Enhanced sarcoplasmic reticulum efficiency in calcium handling improves both systolic and diastolic function in hyperthyroidism. Thyroid hormone also increases the rate of diastolic depolarization and reduction of action potential duration in sinoatrial nodal cells. Indirectly, thyroid hormones increase numbers and affinity of myocardial adrenergic receptors.

CLINICAL SIGNS. Changes in heart rate, myocardial contractility, and ventricular size and mass are associated with excess or reduced serum thyroid hormone concentrations.[27, 28] Cardiovascular manifestations of hypothyroidism include slow heart rate, muffled heart sounds, hypertension (threefold increased incidence over euthyroid human controls), weakened cardiac apex beat and femoral arterial pulses, arrhythmias including atrial fibrillation, and occasionally congestive heart failure.[29] Myxedema is recognized in dogs but has not been associated with pericardial effusion as in humans.[25]

Derangements in serum lipid and cholesterol predispose to atherosclerosis (Fig. 33–4).[25] In a series of 21 affected dogs,[30] all had coronary artery atherosclerosis and myocardial fibrosis; all had small thyroid glands—19 with abnormal histologic changes. Each of the six dogs tested for hypothyroidism had abnormally low serum thyroid hormone concentrations.

Reported ECG changes include low voltage complexes, bradycardia, occasional arrhythmias, conduction disturbances, widened QRS complexes, and T-wave alterations.[25, 26, 29] Myocardial dysfunction may be evident on echo by diminished shortening fraction, myocardial thinning, and alterations of systolic and diastolic time intervals.[25, 26, 31] Right- and left-sided heart filling pressures are typically normal, and heart failure is uncommon in the absence of underlying cardiac disease.[25, 29] Reversible echo changes were demonstrated in long-standing human myxedematous hypothyroidism, and they were compatible with those of idiopathic hypertrophic subaortic stenosis.[32]

THERAPY. Treatment involves thyroid hormone supplementation. If hypothyroidism complicates (or possibly causes) heart failure, standard therapy for heart failure is instituted with thyroid supplementation.

FIGURE 33–4

Coronary atherosclerosis in a 2-year-old male Doberman pinscher with hypothyroidism and hypercholesterolemia. (Reprinted with permission from Atkins CE: The role of noncardiac disease in the development and precipitation of heart failure. Vet Clin North Am 21:1035, 1991.)

HYPERTHYROIDISM

This is the most frequently encountered feline endocrinopathy[32a] but is rare in dogs[32b] (chapter 34).

ADRENAL GLAND

HYPOADRENOCORTICISM (ADDISON'S DISEASE)

Diminished adrenal gland function may result in reduced serum glucocorticoid and/or mineralocorticoid concentrations. Affected dogs are generally young to middle-aged and typically female.[33] Affected cats are young to middle-aged without gender preponderance.[34]

ETIOLOGY. Hypoadrenocorticism may be due to primary adrenal dysfunction, or it may be secondary to adrenocorticotropic hormone (ACTH) deficiency.[29] Clinical manifestations are usually attributable to lack of both hormones.

PATHOPHYSIOLOGY. Cortisol is gluconeogenic and catabolic, has anti-insulin activity, stimulates erythropoie-

sis, and diminishes gut calcium absorption by interfering with vitamin D activity; it maintains vascular integrity and responsiveness to circulating vasoconstrictors. Aldosterone increases serum sodium (which affects extracellular fluid volume) and decreases serum potassium concentrations.[27] Adrenal insufficiency is associated with diminished intravascular volume; reduced heart rate, cardiac output, and peak left ventricular work; and diminished O_2 consumption. It may lead to cardiovascular collapse and death.[29]

CLINICAL SIGNS. These usually relate to the effects of cortisol and/or mineralocorticoid deficiency. Waxing and waning anorexia, vomiting and diarrhea, dehydration, weakness, and bradycardia are common. In severe cases, hypovolemia, shock, collapse, hyperkalemia, and death may ensue.[29] Clinical pathology abnormalities include hyponatremia, hyperkalemia, hypercalcemia, nonregenerative anemia, lymphocytosis, eosinophilia, hypoglycemia, azotemia, and metabolic acidosis. Less commonly, isolated hypocortisolism may occur. Clinical signs are similar but generally less severe, although profound hypoglycemia with seizures may result. Serum sodium and potassium concentrations are usually normal. In affected cats, lethargy, anorexia, weight loss, emesis, polyuria, dehydration, and collapse have been reported. Clinical pathology includes hyponatremia, hyperkalemia, hypochloremia, azotemia, and hyperphosphatemia. Weak pulses, dehydration, and sinus bradycardia may be detected.[34] Myocardial failure has been recorded in cats with low resting and post-ACTH plasma cortisol concentrations and eosinophilia, and without typical electrolyte alterations.[35] These had echocardiographic changes similar to those of dilated cardiomyopathy, were taurine unresponsive, and responded to corticosteroids.

Cardiac manifestations reflect volume depletion (weakness, hypotension). Thoracic radiographs show microcardia and hypoperfused lung vasculature. Electrocardiographic alterations may be dramatic, with mineralocorticoid and glucocorticoid insufficiency, and are characteristic of hyperkalemia (see Hyperkalemia later; also see Fig. 6–30).[27, 29] The ECG changes do not directly relate to serum K^+ concentration because coexistent hyponatremia, hypocalcemia, and acidosis influence the electrocardiogram. Arrhythmias were recorded in 46 of 100 addisonian dogs in one study, and included sinoventricular rhythm, brady- and tachyarrhythmias, conduction disturbances, ventricular fibrillation, and asystole.[29] In a larger study that evaluated pretreatment ECGs in 122 dogs, atrial standstill occurred in about 47 percent, bradycardia in 29 percent, atrial or ventricular extrasystoles in 6 percent, and AV block (second or third degree) in 5 percent.[35a] Another report of a larger population recorded that heart failure was a rare sequela,[35, 36] although death usually results from cardiogenic shock and hyperkalemia. Electrocardiographic changes are generally absent with isolated hypocortisolism.[29]

THERAPY. Management of shock, repletion of gluco- and mineralocorticoids, and restoration of normal electrolyte concentrations are primary concerns. Administration of large volumes of normal saline is advocated for fluid, sodium, and chloride repletion. For life-threatening hyperkalemia, additional therapy to decrease or counteract the effects of elevated serum K^+ includes administration of (1) 5 percent dextrose in water, with or without insulin (0.25 to 0.5 unit of regular insulin/kg with 2 gm of dextrose/unit of insulin), or (2) 10 percent calcium gluconate (1 ml/kg IV over 5 to 10 minutes), or (3) sodium bicarbonate (1 to 2 mEq/kg IV). Mineralocorticoid and glucocorticoid replacements are given.

HYPERADRENOCORTICISM (CUSHING'S SYNDROME)

Spontaneous hyperadrenocorticism results from excessive cortisol production by the adrenal cortex. It is common in the older dog, but feline cases are relatively rare.[29, 37]

ETIOLOGY. Canine hyperadrenocorticism may occur secondary to pituitary adenoma (85 to 90 percent of cases), or be primary, associated with benign or malignant functional adrenal tumors.[29] Feline hypoadrenocorticism is usually associated with diabetes mellitus and pituitary adenomas.[37]

PATHOPHYSIOLOGY. Hypertension is very common (chapter 35).[29] This is thought to be associated with increased sodium and water retention, increased vascular sensitivity to vasopressors such as epinephrine, and cortisol-induced activation of the renin-angiotensin system.[27] Hyperlipidemia and hypercholesterolemia probably contribute to atherosclerosis. In humans, heart failure may be associated with hyperadrenocorticism, probably related to hypertension and potentiation of atherosclerosis.[12, 27]

CLINICAL SIGNS. Polydipsia/polyuria, dermatologic changes, lethargy, muscle wasting, and panting occur.[29] Clinical pathology findings include lymphopenia, eosinopenia, low urine specific gravity, hyperlipidemia, hypercholesterolemia, elevated serum liver enzyme activities, hyperglycemia, and abnormal cortisol response to ACTH or dexamethasone.

Cushingoid dogs may have radiographic and ECG evidence of cardiomegaly,[29] are often advanced in age, and frequently have concurrent chronic acquired valvular disease, especially mitral regurgitation. Pulmo-

nary thromboembolism can cause right-sided heart strain, respiratory failure, or death.

PRIMARY ALDOSTERONISM (CONN'S DISEASE)

Although reported in humans, this condition is rare in dogs and cats.

PATHOPHYSIOLOGY. Aldosterone regulates electrolyte excretion through renal sodium retention and potassium excretion and thus affects intravascular volume. Excessive aldosterone secretion is reported in humans from adrenal adenomas producing hypernatremia, hypokalemia, and systemic hypertension.[12, 27]

CLINICAL SIGNS. Cardiovascular manifestations include left ventricular hypertrophy secondary to increased systemic vascular resistance. Electrocardiographic changes in humans consist of arrhythmias, T-wave alteration, U-wave prominence, and patterns suggesting left ventricular enlargement.[27] I have observed an aged cat with adrenal gland adenoma and primary aldosteronism with hypertensive retinopathy, anorexia, weight loss, hypokalemia, and hypernatremia. Cardiovascular manifestations included a murmur, systolic and diastolic hypertension, left ventricular hyperkinesis and concentric hypertrophy, and nonsustained AV dissociation with junctional tachycardia, modest Q-T interval prolongation, and prominent U waves (Fig. 33–5). Other reports include a dog with idiopathic hyperaldosteronism with borderline systemic hypertension, hypernatremia, and mild hypokalemia;[38] and an aged cat with primary hyperaldosteronism secondary to an adrenal cortical adenocarcinoma, with severe hypokalemia, AV conduction abnormaiities, prolonged PR and QRS intervals, and paroxysmal ventricular tachycardia.[39]

PHEOCHROMOCYTOMA

Catecholamines secreted in excess may exert important adverse effects on the cardiovascular system.

ETIOLOGY. A syndrome associated with catecholamine-producing tumors of the adrenal medulla is rare in humans and animals, but cardiac manifestations can be profound.[27, 40, 41] Affected dogs are most often aged, with no breed or gender predisposition.

PATHOPHYSIOLOGY. Pheochromocytoma can cause local vascular invasion (renal, adrenal, and hepatic vessels) and metastasis, or it can effect changes by catecholamine excretion. In a series of 13 affected dogs, right and left adrenal glands were affected with equal frequency; bilateral involvement was noted in one dog. Adrenal tumors were invasive in eight dogs; in five, the caudal vena cava was involved, producing obstruction and ascites in two of the five. Two of the eight had distant metastases.[41] Catecholamines that are secreted constantly, episodically, or both[27] may cause hypertension, "cardiomyopathy of overload,"[2] arrhythmias, ischemic myocarditis, or cardiomyopathy.[27]

CLINICAL SIGNS. These may be associated with local invasion, distant metastases, or the effects of endogenous catecholamine release. In dogs, the clinical pre-

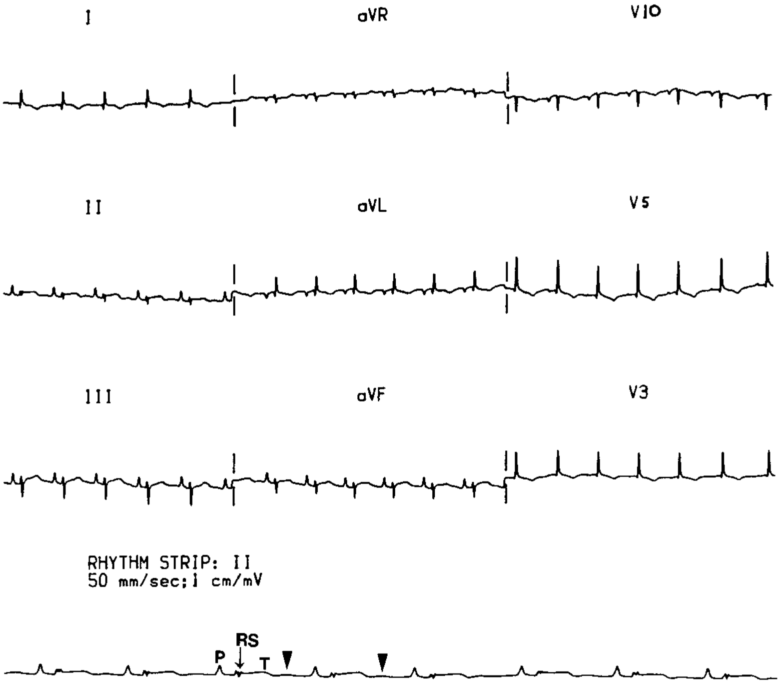


FIGURE 33–5

Electrocardiogram from an aged cat with primary hyperaldosteronism, hypokalemia, and hypertension. The QT interval is prolonged (190 msec), and a left axis deviation is present. Note the presence of U waves *(arrowheads)* following the T waves. P wave and an RS complex are indicated. (Courtesy of Dr. John Rush. Reprinted with permission from Atkins CE: The role of noncardiac disease in the development and precipitation of heart failure. Vet Clin North Am 21:1035, 1991.)

sentation may include anxiety, anorexia, hyperthermia, panting, cough, dyspnea, weakness, trembling, mydriasis, hypertensive retinopathy, proteinuria, polyuria, polydipsia, neurologic dysfunction, epistaxis, cyanosis, flushing of pinnae, diarrhea, abdominal distention, collapse, and death.[40, 41] Hypertension is identified in approximately 50 percent of affected dogs in which blood pressure is measured.[40] ECG changes include left ventricular enlargement and atrial and ventricular arrhythmias. Arrhythmias, including sinus tachycardia, are present in 15 to 54 percent of the cases.[40, 41] In 13 affected dogs, sudden death was reported in 6 of 8 symptomatic animals.[41] The other five dogs were asymptomatic, with pheochromocytoma detected as an incidental postmortem finding.

Cardiovascular manifestations documented in people include systemic hypertension, which is often intermittent; ECG abnormalities in up to 75 percent of patients (T-wave inversion, LV hypertrophy, shortened P-R and QRS intervals, S-T segment alterations, sinus tachycardia, and other arrhythmias); echocardiographic changes (LV hypertrophy, systolic anterior mitral valve motion during hypertensive crises, and, typically, normal ventricular function); myocarditis; reversible cardiomyopathy; and heart failure.[27] Myocardial injury is associated with excess catecholamines and related systemic hypertension, ischemia, coronary vasoconstriction, increased sarcoplasmic permeability, and intracellular calcium overload.[27]

THERAPY. Life-threatening arrhythmias are managed with standard antiarrhythmic therapy, alone or in conjunction with α-adrenergic blocking agents (e.g., phenoxybenzamine) and β-adrenergic blocking agents (e.g., propranolol), after phenoxybenzamine has been administered. Surgical removal of the adrenal tumor is the definitive treatment.

HYPERSOMATOTROPISM (ACROMEGALY)

Growth hormone influences many metabolic activities and, when secreted in excess, may cause cardiovascular manifestations.

ETIOLOGY. Growth hormone (somatotropin) excess is most often associated with functional pituitary adenomas in humans and cats. In dogs it may occur secondarily in females after pituitary stimulation during excessive or prolonged progesterone exposure.[27, 29] Affected dogs and cats are of advanced age (mean, 10 years). No breed predilection is recognized, but male cats appear to be predisposed.[29, 42, 43]

PATHOPHYSIOLOGY. Growth hormone and the insulin-like growth factors (somatomedins) that it stimulates produce a variety of biologic effects. The most important include stimulation of protein synthesis and reduced protein catabolism, reduced glucose utilization, enhanced glycogen deposition, and lipolysis. Growth hormone is a potent diabetogenic hormone, and diabetes mellitus is the most commonly associated clinical syndrome. Other manifestations of acromegaly include proliferation of bone, cartilage, soft tissues, and internal organs, including the heart.[42] Acromegalic humans have cardiomegaly, focal interstitial myocarditis and fibrosis, accelerated coronary atherosclerosis, hypertension, increased cardiac mass, cardiac failure, and arrhythmias. Heart disease and failure is related in part to hypertension and coronary artery disease and probably is due to a direct cardiotoxic effect of growth hormone.[27]

CLINICAL SIGNS. Respiratory stridor secondary to soft tissue impingement on airways is the most common clinical manifestation of acromegaly. Enlargement of limbs, feet, abdomen, and head is usually noted. Pyometra and associated mammary nodules may occur in progestogen-induced hypersomatotropism. Neurologic signs may accompany pituitary tumors. Also reported are hyperglycemia, glucosuria, hyperlipidemia, hyperinsulinemia (or later hypoinsulinemia), abnormally high growth hormone or somatomedin concentrations, elevated serum liver enzyme activities, leukocytosis, hyperphosphatemia, and variable changes in the erythron.[42]

In six diabetic cats reported with acromegaly and high serum growth hormone concentrations, five had hypertrophic cardiomyopathy and three died of left heart failure.[29, 43] Systolic murmurs, gallop rhythms, muffled heart sounds, dyspnea, and ascites were variably present. Thoracic radiographs disclosed cardiomegaly, pleural effusion, and pulmonary edema.[29, 43] A similar case was reported in a 12-year-old castrated male cat with hypersomatotropism, pleural effusion, hypertrophic cardiomyopathy, hyperinsulinemia, and mild glucose intolerance but without acromegaly or diabetes mellitus.[44] In a series of 31 cats with hypertrophic cardiomyopathy, mean serum growth hormone concentration was significantly greater (approximately fourfold) than that in normal cats and those with other cardiac disease, with 61 percent having concentrations above the expected normal range.[45] Eight of these cats underwent postmortem examination. None had pituitary tumors. Furthermore, none were diabetic, and plasma insulin concentrations were normal. A retrospective review of 74 cats with hypertrophic cardiomyopathy[46] revealed them to be substantially younger (mean, 5.6 ± 2.9 years; range, 1 to 16) than cats reported with "classic" hypersomatotropism (mean, 10 years; range, 8 to 14).[29] These observations require further investigation, and cause-effect relationships between hypersomatotropism and feline cardiovascular disease require further study.

Cardiomegaly, but not heart failure, has been recognized in dogs with growth hormone excess.[29]

DIABETES MELLITUS

Insulin is released from pancreatic β-cells in response to blood glucose elevation or stimuli from other secretagogues such as amino acids. This anabolic hormone stimulates glucose entry into cells, glycogenesis, and lipogenesis. It opposes gluconeogenesis, lipolysis, ketogenesis, and the secretion and effects of glucagon.

PATHOPHYSIOLOGY. Relative or absolute deficiency in pancreatic insulin secretion produces glucose intolerance, hyperglycemia, glucosuria, and an array of systemic and metabolic aberrations. These include hyperlipidemia, hypercholesterolemia, hyperglucagonemia, hepatic lipidosis, serum liver enzyme activity elevation, ketosis, acidosis, weight loss, hyperosmolality, neuropathy, retinopathy, glomerulopathy, and cardiovascular disease.

In human type I and II diabetes, the incidence of hypertension and coronary atherosclerosis is higher than in nondiabetics.[27, 47] Idiopathic cardiomyopathy is more frequently recognized in human diabetics.

Diabetic cardiomyopathy is associated with microvascular disease, prolonged diabetic state, and histologic cardiac lesions (hypertrophy, fibrosis, glycoprotein accumulation, and coronary microvascular endothelial and subendothelial proliferation).[47, 48]

Various metabolic and structural mechanisms are associated with diabetes-related systolic and diastolic dysfunction. These include alterations in sarcolemmal membrane integrity secondary to cholesterol deposition and diminished sialic acid concentrations—both related to chronic insulin insufficiency.[49] These effects threaten myocyte viability and increase intracellular calcium concentrations. The latter alter diastolic myocardial function and the organelle integrity, as well as activate destructive enzymes. Increased sympathetic activity in diabetics may further contribute to cardiac dysfunction. Animal studies indicate that the diabetic heart has increased sensitivity to the deleterious effects of hypertension.

Diastolic dysfunction has been demonstrated in human diabetics. Functional changes include elevated left ventricular end-diastolic pressure, reduced ejection fraction and left ventricular fractional shortening, systolic time interval abnormalities, and increased wall stiffness.[27, 47, 48] Diabetic control is thought to diminish the risk of diabetic cardiomyopathy. However, two recent studies emphasize the mild nature of diabetic cardiomyopathy in the absence of coronary macrovascular disease and hypertension.[50, 51] An increased risk of hypertension or coronary artery disease has not been demonstrated in diabetic dogs. Only mild decreases in left ventricular systolic function were present in canine alloxan-induced diabetes of less than 5 years' duration (Fig. 33–6).[48] In addition, a significant inverse correlation between glycosylated hemoglobin (increasing values indicating inferior control) and left ventricular fractional shortening was demonstrable. Changes in diastolic performance have been mild and less consistent. Collectively, these findings corroborate recent studies in humans suggesting that diabetic cardiomyopathy, in the absence of coronary heart disease and hypertension, is mild.

CLINICAL SIGNS. Although cardiac failure due to diabetes mellitus may not occur in animals, reduced cardiac performance in diabetics may complicate underlying pre-existing heart disease.

Peripheral neuropathy may cause significant mor-

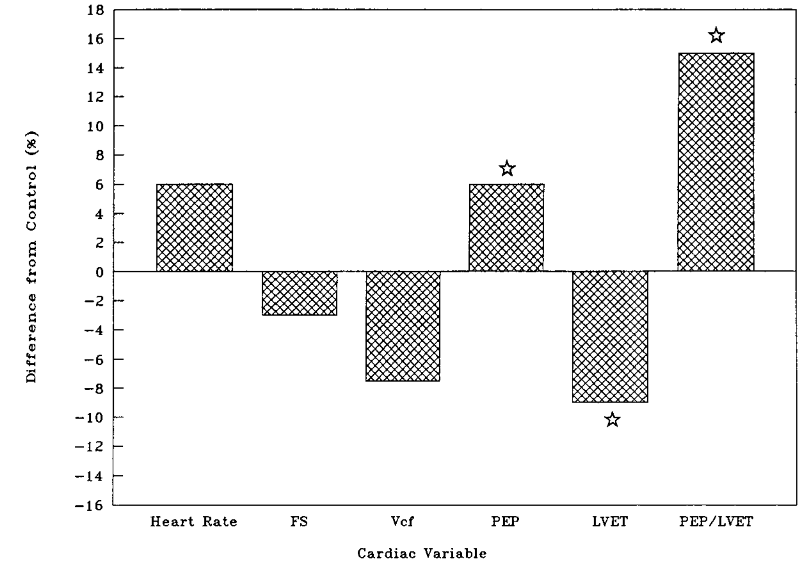


FIGURE 33–6

Cardiovascular parameter displayed as percentage difference from controls in alloxan-induced diabetic dogs. Mild cardiomyopathy is indicated by significant ($p < .05$; stars) changes in pre-ejection period *(PEP)*, left ventricular ejection time *(LVET)*, and *PEP/LVET*. *FS*, fractional shortening; *Vcf*, velocity of circumferential fiber shortening. (Reprinted with permission from Atkins CE: The role of noncardiac disease in the development and precipitation of heart failure. Vet Clin North Am 21:1035, 1991.)

bidity in diabetic humans.[27,52] Parasympathetic dysfunction typically precedes sympathetic dysfunction. The cardiovascular effects of diabetic autonomic neuropathy may antedate other dysfunction and include increased heart rate; diminished responsiveness to vagal maneuvers and pharmacologic autonomic perturbation; arrhythmias; cardiac denervation; postural hypotension; increased anesthetic-related cardiopulmonary arrest; and 5-year mortality.[27,52] Although peripheral neuropathy has been documented in diabetic dogs[53] and cats,[54] ECG studies of alloxan-diabetic dogs showed no evidence of impaired parasympathetic autonomic function,[52] suggesting that the dog is relatively resistant to neuropathic effects of diabetes.

GLYCOGEN STORAGE DISEASE

Inborn errors of metabolism may cause a variety of derangements, some with cardiovascular effects.

ETIOLOGY. Deficiency of lysosomal acid alpha-glucosidase has produced cardiac and skeletal myopathies (Pompe's disease or type II glycogen storage disease) in the Lapland dog.[55,56] All affected dogs have been of this breed, suggesting a hereditary basis.

PATHOPHYSIOLOGY. Abnormalities of myocardial diastolic or systolic function may result from myocardial cellular infiltration by incompletely degraded macromolecules such as glycogen.

CLINICAL SIGNS. Affected dogs may display muscular weakness, polydipsia, vomiting, megaesophagus and regurgitation, dyspnea (due to inhalation pneumonia), dysphonia, panting, and death before 2 years of age. Cardiac findings include atrial fibrillation, ventricular ectopy, tall R waves, wide QRS complexes, and shortened PR intervals.[55] Postmortem changes include cardiomegaly with focal myocarditis and extensive glycogen infiltration. Congestive heart failure was not present.

ELECTROLYTE ABNORMALITIES

Abnormal ECGs may be recorded in animals with structurally normal hearts but who have significant electrolyte or acid-base alterations. Thus, ECGs are useful to help diagnose and manage many extracardiac conditions (Fig. 33–7).

CALCIUM

Calcium (Ca^{++}) plays an important role in excitation and contraction of cardiac muscle fibers as well as maintaining normal vascular reactivity. ECG changes are associated with effects of Ca^{++} ions on the transmembrane action potential. Hypercalcemia shortens the duration of phase 2; hypocalcemia prolongs the duration of phase 2 of the action potential.

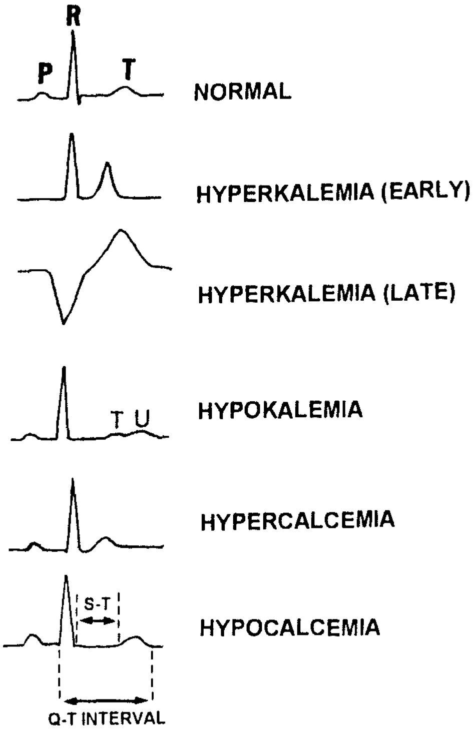


FIGURE 33–7

Examples of the effects of electrolyte abnormalities on the electrocardiogram. *Hyperkalemia:* Early ECG changes include a tall, peaked ("tented") T wave, usually symmetric; a normal or decreased Q-T interval; P-R interval prolongation with reduction in P wave amplitude followed by loss of the P wave. Late ECG changes include progressive decrease in R wave amplitude with increased prominence of an S wave, widening of the QRS complex, S-T segment depression, and depressed intraventricular conduction. *Hypokalemia:* There may be gradual ST segment depression, with a prominent U wave following and fusing with the T wave. In clinical practice, however, these changes are uncommonly detected until life-threatening hypokalemia is present. *Hypercalcemia:* The Q-T interval is prolonged. *Hypocalcemia:* The S-T segment is shortened, although the correlation between serum Ca^{++} concentration and Q-T interval is unpredictable (Q-T interval is also affected by heart rate). See text for details. (Courtesy of Dr. Philip Fox.)

HYPERCALCEMIA

Serum Ca^{++} greater than 12 mg/dl (> 11 mg/dl in cats) indicates hypercalcemia. Associated disorders include paraneoplastic syndromes, hypoadrenocorticism, hyperparathyroidism, and atypically, renal failure.[29] Cardiovascular manifestations relate predominantly to ECG alterations and include S-T segment depression and shortened Q-T interval. The latter does not correlate linearly with serum calcium concentrations, however. Slowed intracardiac conduction and AV block have been noted with severe hypercalcemia.[29]

THERAPY. Management of hypercalcemia depends, in part, on the underlying cause. When caused by paraneoplastic syndromes related to neoplasia, surgical or medical management is warranted. When associated with hypoadrenocorticism, corticosteroid and saline therapy is indicated. Acute reduction of serum calcium concentrations is indicated when the calcium times phosphorus product is greater than 60. This is accomplished with volume expansion (normal saline), glucocorticoids (prednisolone, 1 to 1.5 mg/kg PO bid), and/or furosemide (2 to 4 mg/kg sid to bid PO).

HYPOCALCEMIA

A serum Ca^{++} concentration of less than 6.5 mg/dl indicates hypocalcemia. Associated causes include chronic renal failure, hypoparathyroidism, hypoalbuminemia, acute pancreatitis, and puerperal tetany. Acute, severe hypocalcemia may follow bilateral thyroidectomy for feline hyperthyroidism if parathyroid glands are inadvertently removed or injured. Hypocalcemia (unlike hypercalcemia) is associated with diminished cardiac performance and heart failure in humans.[57] It has been postulated that myocardial β-receptor "down regulation" occurs in dilated cardiomyopathy, which may render the myocardial contractile state dependent on extracellular Ca^{++} concentration.[58] With stable chronic renal failure in humans, graded increases in serum Ca^{++} (1.02 to 1.68 mmol/L) produced clinically significant improvement in myocardial contractility.[59] I have observed reversible myocardial depression in a dog with neurogenic pulmonary edema secondary to hypocalcemic seizures and hypoparathyroidism. The exact role of hypocalcemia in the myocardial dysfunction was not clear.

Hypocalcemia prolongs phase 2 action potential duration. The ECG changes classically include Q-T interval and S-T segment prolongation (see Fig. 33–7). Tachycardia, tall R waves, and T-wave abnormalities have been reported.

THERAPY. Treatment of hypocalcemia is unnecessary if it is associated with hypoalbuminemia. Calcium supplementation is required if hypocalcemia causes profound weakness, cardiac hypokinesis, or tetany. Acutely, 10 percent calcium gluconate (1 to 1.5 mg/kg) may be infused intravenously over 10 to 20 minutes with continuous ECG monitoring. In nonemergency situations, or after stabilization, oral calcium and vitamin D are administered.

POTASSIUM

Cardiac cells take up potassium (K^+) and eject sodium to maintain the resting negative membrane potential. Different cardiac cells vary in excitability and conduction in response to extracellular K^+. The sinus node and His bundle are more resistant than ventricular myocardium to increases in extracellular K^+, which in turn is more resistant than atrial myocardium. Neither hyper- nor hypokalemia produces or aggravates heart failure, other than by inducing or worsening arrhythmias. Experimentally, the inotropic and lusitropic response to epinephrine and preloading was significantly greater (20 to 60%) in normal versus hypokalemic dogs.[60]

HYPERKALEMIA

The ECG manifestations of hyperkalemia (>5.5 mEq/L) include sinus bradycardia; tall, peaked T waves; P waves with low amplitude, widened, and eventually absent; prolonged P-R and QRS intervals and heart rate–corrected Q-T interval; and, generally, low amplitude QRS complexes (Fig. 33–7). Although ECG changes generally worsen with increasing serum potassium concentrations, the exact prediction of serum potassium concentration from the ECG is impossible because of coexistent acid/base and electrolyte derangements (see Hypoadrenocorticism section earlier). Common etiologies of hyperkalemia include metabolic acidosis, hypoadrenocorticism, massive cellular injury, renal failure, obstructive uropathy, untreated diabetic ketoacidosis, and poor tissue perfusion.

THERAPY. Treatment is directed to reduce severe serum potassium elevation by administration of (a) 5 percent dextrose in water with or without insulin (0.25 to 0.5 unit of regular insulin/kg with 2 gm of dextrose/unit of insulin); (b) 10 percent calcium gluconate (1 ml/kg IV over 5 to 10 minutes); or (c) sodium bicarbonate (1 to 2 mEq/kg IV). Treatment also consists of resolution of the underlying disease.

HYPOKALEMIA

Common causes of hypokalemia (< 3.5 mEq/L) include excessive fluid therapy, gastrointestinal or urinary K^+ loss, intensive diuretic therapy, alkalosis, anorexia (especially cats), hyperaldosteronism, and correction of diabetic ketoacidosis.[29] ECG changes include nonsustained AV dissociation, modest Q-T interval prolongation, T-wave alteration, and prominent U waves (see Figs. 33–5 and 33–7). In humans suffering myocardial infarction, the incidence of ventricular arrhythmias, including fibrillation, is significantly greater, with concomitant hypokalemia.[61]

THERAPY. Treatment involves (1) potassium supplementation and (2) correction of the underlying cause of hypokalemia. Supplemental potassium may be provided (a) orally by dietary modification (e.g., nuts or fruits) or commercial preparations (potassium gluco-

nate: dogs, 2.2 mEq per 100 kcal daily caloric intake; cats, 2 to 6 mEq/day) or (b) parenterally. A commonly used guideline for intravenous supplementation is based on serum potassium concentration. For a serum concentration of less than 2.0 mEq/L, give 80 mEq/L of fluid; 2 to 2.5, give 60; 2.6 to 3.0, give 40; and 3.1 to 3.5 mEq/L, give 25 to 30 mEq/L. Intravenous potassium supplementation should not be administered at greater than 0.5 mEq/kg/hour.

MAGNESIUM

Hypermagnesemia may shorten the Q-T interval and delay intracardiac conduction. Experimental hypomagnesemia is associated with focal myocardial necrosis and arrhythmias. In clinical settings, it has been associated with ventricular ectopy.[61–63]

Reported abnormalities may be related to the interrelationships of magnesium (Mg^{++}) with Ca^{++} and K^+. Intracellular K^+ repletion is prevented by hypomagnesemia. Additionally, chronic hypomagnesemia increases cytosolic and mitochondrial Ca^{++} concentrations and has been associated with cardiomyopathy in experimental animals. Hypermagnesemia interferes with calcium influx and intracellular action, thereby producing a negative inotropic effect.[62] Hypomagnesemia occurs commonly in people treated for heart failure with diuresis and anorexia. Furthermore, subnormal tissue and serum Mg^{++} concentrations complicate 40 percent of human heart failure cases. Nevertheless, disturbances in Mg^{++} metabolism are not established in the genesis or precipitation of heart failure other than in a potential arrhythmogenic role. Moreover, serum K^+ or Mg^{++} concentrations do not accurately reflect tissue ion levels.[61]

THERAPY. For treatment of hypomagnesemia and ventricular arrhythmias, magnesium sulfate can be administered orally (dog: 8 to 25 gm/day; cat: 2 to 5 gm/day) or intravenously (25 mg/kg IV of 50% solution, diluted, over 30 minutes).

RENAL DISEASE

UREMIC CARDIOMYOPATHY

In humans, end-stage renal failure may increase LV stroke work index, cardiac dimensions, and end-diastolic pressure and predispose to heart failure. Cardiac dysfunction may complicate protein-losing glomerulopathy related to systemic hypertension (pressure overload), anemia (volume overload), and pulmonary thromboembolism (pressure overload). Although the hypothesis is controversial, the syndrome of uremia has been suggested to produce direct cardiotoxic effects.[64] To my knowledge, this syndrome has not been recognized in companion animals. "Uremic endocarditis" has been described in two of eight dogs with uremic pericarditis and soft tissue mineralization.[65]

UREMIC PERICARDITIS

Acute and chronic uremia produces pericardial inflammation in one third to one half of humans presented for dialysis.[64]

PATHOPHYSIOLOGY. Pathogenesis involves development of serositis secondary to uremic toxins and, possibly, to volume overloading.

CLINICAL SIGNS. Pericarditis may cause fever. A friction rub is sometimes detected during auscultation. Chest radiographs and ECG are abnormal in the majority of affected humans, and heart failure occurs up to 70 percent of the time. Less common complications of uremia in humans include fibrinous pleuritis, chronic constrictive pericarditis, and hemorrhagic tamponade associated with heparinization for dialysis.[64]

In a series of 66 cats with necropsy evidence of pericardial disease, pericardial effusion was associated with renal dysfunction in 7 (11%); 4 cats had chronic end-stage renal disease with probable hypertension; 1 was similarly affected, but without LV hypertrophy, suggesting early or no hypertension; 1 had acute renal failure (ethylene glycol intoxication); and 1 had glomerulonephritis with hypoalbuminemia.[66] In 42 dogs with pericardial effusion, uremic pericarditis was identified in 1 animal.[67] Another study revealed pericardial lesions in 11 of 150 dogs (7%) with renal failure; 8 had clear or sanguineous pericardial effusion; and 3 had pericarditis.[65]

THERAPY. Management of pericardial effusion may entail pericardiocentesis and/or pericardiectomy. In acute syndromes, successful treatment of underlying renal disease or institution of dialysis resolves uremic pericardial effusion in 3 to 10 days; however, less than 50% of chronic human cases resolve. Therapies using nonsteroidal anti-inflammatory drugs and corticosteroids (systemic and intrapericardial) have been advocated.[64]

GASTROINTESTINAL DISEASE

PANCREATITIS

Pancreatitis may cause a variety of systemic and metabolic abnormalities. However, clinically important cardiac dysfunction is rare.

ETIOLOGY. Inciting causes vary and are usually unknown. Diagnosis is often hindered by lack of specific laboratory tests.

PATHOPHYSIOLOGY. Acute canine hemorrhagic pancreatitis has been associated with pulmonary hypertension, possibly due to release of vasoactive substances.[68] Whether this pulmonary hypertension is sustained or is of clinical importance is not known. A myocardial depressant factor (MDF) has been postulated to be associated with acute hemorrhagic pancreatitis.[69] Pancreatic ischemia promotes release of this peptide, which has a negative inotropic effect, thereby lowering cardiac output. Pancreatic enzymes may also damage the myocardium directly or induce coronary arterial thrombi. Electrolyte disturbances contribute to the genesis of supraventricular and ventricular arrhythmias, interventricular conduction disturbances, and S-T segment changes.

CLINICAL SIGNS. Acute hemorrhagic pancreatitis may lead to irreversible shock associated with cardiac dysfunction, endotoxemia, sepsis, hypovolemia, and peripheral vasodilation. Congestive heart failure *per se* is not a recognized complication, but ventricular and supraventricular arrhythmias are common.

THERAPY. Treatment is directed toward generalized patient support, including fluid therapy, antibiotics, and antiarrhythmic drugs when needed.

GASTRIC DILATATION–VOLVULUS

Cardiac manifestations are common and frequently serious in GDV. A mortality rate of 43 percent was reported in one study, due in part to cardiac dysfunction, endotoxemia, hypovolemia, shock, and disseminated intravascular coagulation.[70]

ETIOLOGY. Many theories have been proposed. The majority of cases occur in large, deep-chested dogs.

CLINICAL SIGNS. Cardiac arrhythmias are common and most often develop after surgical decompression. They include atrial and ventricular extrasystoles and tachycardias, atrial fibrillation, and, uncommonly, bradyarrhythmias. In 48 GDV-related arrhythmias, 19 percent were detected at admission, 18 percent were recorded intraoperatively, and 65 percent were noted postoperatively.[70]

PATHOPHYSIOLOGY. A number of mechanisms may be operative: myocardial ischemia caused by GDV-induced hypotension and tachycardia-induced reduction in diastolic filling and coronary perfusion time; autonomic imbalance; fluid, electrolyte, and acid-base perturbation; and release of myocardial depressant factor. Postmortem myocardial lesions are frequently noted and are probably associated with ischemia and arrhythmias. Myocardial degeneration, necrosis, and, rarely, fibrosis were reported in 62 percent of 13 dogs dying with GDV.[71] Seventy-seven percent of these dogs had arrhythmias. In experimental GDV, six (75 percent) of eight dogs suffered subendocardial necrosis, with four of these six dogs developing ventricular arrhythmias.[72]

Experimental GDV has been associated with a reduction in a number of hemodynamic variables: cardiac output (by 64 to 89 percent); LV dP/dt (42 percent); LV end-diastolic pressure (68 percent); mean arterial pressure (45 to 48 percent); total peripheral resistance (33 percent); coronary blood flow (50 percent); and myocardial oxygen consumption (50 percent).[72] Decompression improves loading conditions and returns cardiac output toward normal, despite the release of myocardial depressant factors.[72–74]

Myocardial depressant factor is a polypeptide (molecular weight less than 1000) thought to be released from ischemic pancreas during shock. It results in negative inotropy, splanchnic vasoconstriction, and reticuloendothelial system dysfunction.[74] Both cardiostimulatory and cardioinhibitory humoral factors are released after decompression in canine GDV, and the net effect in most dogs is diminished cardiac performance. Because of alterations in loading conditions, exact statements about the effect of GDV on cardiac contractility are impossible. However, since dP/dt/aortic opening pressure (a relatively load-independent index of myocardial performance) is elevated in GDV, enhanced contractility is suspected.[74] This state, probably mediated through the sympathetic nervous system, is counteracted by alterations in heart rate and rhythm, reduced preload, and increased afterload, with a net reduction in cardiac output. After decompression, dP/dt/aortic opening pressure rose in two dogs and fell precipitously in four dogs with experimental GDV. Plasma from the latter four dogs had evidence of myocardial depressant factors *in vitro*, whereas the former two had evidence of cardiostimulatory substance(s), probably catecholamines.[74]

CLINICAL SIGNS. GDV does not produce congestive heart failure. However, it may precipitate or worsen failure in dogs affected with heart disease, especially cardiomyopathy. The most characteristic signs are acute abdominal distention and tympany, restlessness, salivation, and rapid, labored breathing. Many dogs present with physical examination findings of shock (rapid pulse, pale mucous membranes, hypotension, prolonged capillary refill time) and arrhythmias.

THERAPY. Treatment is aimed at alleviating gastric distention; reducing the volvulus; correction of fluid, acid-base, and electrolyte disturbances; and controlling

serious arrhythmias. If septic shock is present, corticosteroids (dexamethasone sodium phosphate, 4 mg/kg IV) and antibiotics are indicated. Sodium bicarbonate is reserved for cases with life-threatening metabolic acidosis.

HEPATIC DISEASE

Hepatocellular failure induces reversible systemic vasodilation and enhances cardiac output as much as two to four times.[27] Factors affecting this hyperkinetic state include hypoxemia, which occurs secondary to pulmonary microarteriovenous fistulas, intrahepatic arteriovenous shunting with cirrhosis, and diminished deactivation of vasodilators and estrogens.

CENTRAL NERVOUS SYSTEM

NEUROGENIC HEART DISEASE

Cardiovascular lesions have been reported in association with certain neurologic disorders.

ETIOLOGY. Multifocal myocardial necrosis secondary to brain lesions (ruptured aneurysm, hemorrhage, neoplasia, and meningitis) has been documented in humans.[75] Electrocardiographic abnormalities are also recognized (S-T segment and T-wave changes and Q-T interval prolongation). A similar association between myocardial lesions and brain or spinal cord disease has been documented in each of the domestic species except the cat. Myocardial lesions were identified in a series of 40 dogs with neurologic diseases that included trauma (73%), intervertebral disk protrusion, distemper, neoplasia, and encephalomalacia. Focal subendocardial or subepicardial streaks were identified and corresponded to histologic lesions of swelling and acute degeneration; myonecrosis; and in some cases, inflammation and fibrosis. These dogs ranged in age from 1 month to 12 years. Clinical data were provided on only two dogs, neither of which was in heart failure. One trauma case exhibited ventricular tachycardia and died after postoperative cardiac arrest.

PATHOPHYSIOLOGY. A proposed mechanism is autonomic imbalance, especially with sympathetic overactivity.[75] Norepinephrine infusion can produce similar lesions. Reserpine, which inhibits sympathetic action by depleting norepinephrine tissue stores, protects against myocardial necrosis after head trauma. The pattern of necrosis is similar to that of adrenergic nerve supply and is associated with focal depletion of catecholamine granules. In most instances, the central nervous system insult is acute, and there is a lag period of several days before the onset of myocardial lesions.

HEMATOLOGIC DISEASE

ANEMIA

Anemia is the most common cause of high-output states in humans and may result in high output failure in animals.[76]

PATHOPHYSIOLOGY. Cardiac output increases as diminished blood viscosity (hemoglobin < 7 g/dl) and resultant tissue hypoxia reduce systemic vascular resistance. Increased circulating catecholamines may also contribute by their positive inotropic effect. Eccentric cardiac hypertrophy and increased heart rate accompany this high-output state.

CLINICAL SIGNS. A midsystolic heart murmur, gallop rhythm, and hyperdynamic precordial impulse may be detected. Rarely, pulmonary edema is present. Chronic anemia (PCV < 20 percent) frequently produces soft, midsystolic murmurs in dogs and cats, probably related to changes in viscosity, heart rate, cardiac geometry, and cardiac output. Such murmurs may also reflect unmasked mitral insufficiency. High-output cardiac disease was described in a profoundly anemic kitten with a systolic heart murmur, cardiomegaly, pulmonary edema, and diminished myocardial performance.[77] These signs abated and cardiac anatomy and function normalized after symptomatic therapy and reattainment of a normal erythron.

THERAPY. Correction of the underlying cause of anemia, transfusion, and treating heart failure represent therapeutic goals.

DISORDERS ASSOCIATED WITH INCREASED BLOOD VISCOSITY

POLYCYTHEMIA AND HYPERGLOBULINEMIA

ETIOLOGY. Polycythemia may be related to primary conditions, such as neoplastic processes, or may occur secondary to hypoxemia (lung or cyanotic heart disease) or excessive erythropoietin hormone production from neoplasia or renal disease. Numerous pathologic states result in an increased globulin concentration, especially multiple myeloma in dogs.[78] Hyperviscosity syndromes may result from marked elevation in circulating immunoglobulin concentration in plasma cell dyscrasias or other neoplastic syndromes. A small num-

ber of dogs with hyperviscosity syndrome have been reported.[79–82]

PATHOPHYSIOLOGY. Polycythemia and hyperglobulinemia may contribute to cardiac dysfunction by increasing ventricular afterload.[76] The optimal hematocrit in regard to blood flow is approximately 40 percent. Polycythemic states, despite increased blood viscosity, tend to be accompanied by elevations in blood oxygen content, cardiac output, and blood volume.[76] Little evidence exists in the veterinary literature to indicate that heart failure results from polycythemia. However, polycythemia may well contribute to cardiac dysfunction in cyanotic congenital heart disease.

High-output heart failure has been associated with hyperviscosity syndrome produced by elevated circulating immunoglobulin concentrations in human multiple myeloma.[83–85] Cardiac dysfunction results from increased volume and pressure loading, as well as relative myocardial ischemia due to poor coronary perfusion. In one study, eight of ten patients with hyperviscosity syndrome (mean serum total protein concentration, 13.0 g/dl; mean hemoglobin concentration, 7.7 g/dl) exhibited congestive heart failure.[82] There was no correlation between serum viscosity and the severity of signs. In another report, 8 percent of 535 patients with hyperviscosity syndrome died of heart failure.[83] Multiple myeloma, with only mild anemia and without hyperviscosity, has also been associated with high-output heart failure in humans, characterized by a relative tachycardia, reduced systemic vascular resistance, elevated left- and right-sided venous pressures, and abnormally high cardiac output.[83] The mechanism for high-output failure remains obscure.

CLINICAL SIGNS. In dogs with reported hyperviscosity syndrome, clinical presentation included hemorrhagic diathesis (epistaxis) and renal, cardiac, ocular, and neurologic dysfunction. Of seven reported cases, one dog (a 5-year-old male Yorkshire terrier) was diagnosed as having heart failure.[80] Detectable abnormalities included a holosystolic murmur over the mitral valve region, sinus tachycardia, cardiomegaly, and pulmonary edema. The underlying disease was lymphocytic leukemia (serum total protein, 12.8 g/dl; packed cell volume (PCV), 34%).

THERAPY. The goal of reducing blood viscosity can be attained by phlebotomy, chemotherapy for neoplastic polycythemia or hyperglobulinemia, or plasmapheresis for hyperglobulinemia.

MISCELLANEOUS DISORDERS

HEAT STROKE

When core temperatures exceed 43°C (>109° F) in dogs, direct thermal tissue injury produces heat stroke.[86]

PATHOPHYSIOLOGY. Heat-induced vasodilation reduces systemic vascular resistance, with resultant hypotension and decreased tissue perfusion. This may be complicated by reduced myocardial performance, volume contraction secondary to dehydration, and other fluid-electrolyte and acid-base abnormalities. Subendocardial hemorrhage, myocyte degeneration and necrosis, right ventricular dilatation, and pulmonary edema are reported.[87] The exact role of cardiac dysfunction in the development of pulmonary edema is difficult to determine, since pulmonary edema associated with acute respiratory distress syndrome occurs in heat stroke.[88]

CLINICAL SIGNS. Multiorgan failure may occur, manifested by panting, tachycardia, vomiting, diarrhea, convulsions, hemorrhage, collapse, coma, and death. Renal, hepatic, pulmonary, and cardiac dysfunction may develop. Elevated serum lactate dehydrogenase (LDH) activity is a consistent finding. Sinus tachycardia, T-wave and S-T segment alterations, and conduction disturbances have been documented.[87] Cardiac function has been described as being either hyper- or hypodynamic, the latter potentially producing cardiogenic shock.[86, 87] Heart failure is rare. Right ventricular dilatation and temporary, but prolonged, right ventricular dysfunction have been noted. I have documented reversible myocardial failure and pulmonary edema.

THERAPY. Successful management is aided by rapid recognition and initial temperature reduction using cool water. Ice water may interfere with heat exchange by causing peripheral vasoconstriction. Heat reduction efforts should cease when the body temperature approaches 103° F. Concomitant aggressive isotonic fluid therapy (shock doses: 90 ml/kg/hr), as well as management of metabolic acidosis, secondary sepsis, coagulopathies, arrhythmias, and specific organ system dysfunction, may also be necessary. Corticosteroids (dexamethasone sodium phosphate at 4 mg/kg IV) have been advocated for their membrane-stabilizing effects.

HYPOTHERMIA

Hypothermia occurs with a core body temperature of less than 35°C (< 95° F). It may produce multiple organ dysfunction and mortality rates as high as 80 percent.[89]

PATHOPHYSIOLOGY. There is little information about cardiac effects resulting from hypothermia. Experimental hypothermia in dogs causes a period of increasing cardiac contractility (average maximum increase in contractile force of 101 percent at 27.8°C). In some dogs, this was followed by a fall in contractility (observed in 33 percent of the animals but only at < 20° C);

ventricular fibrillation (in 50 percent of dogs, all at < 23.5° C); hypotension (systolic and diastolic blood pressures fell by approximately 40 percent at 19.5° C); and sinus bradycardia (average heart rate, 31 bpm at 19.5° C).[90] Cardiac contractility actually increased by 26 percent at 19.5°C.

Cardiac dysfunction may be caused by myocardial muscle injury due to associated abnormalities in myocardial microcirculation, aggravated by the increased blood viscosity that occurs with splenic contraction and plasma loss.[89] Metabolic acidosis also depresses myocardial function.

CLINICAL SIGNS. The sinoatrial node is temperature dependent, and reduced heart rates accompany hypothermia. In humans, cardiac manifestations are often reversible and include sinus bradycardia and other arrhythmias, S-T segment changes, regional wall motion abnormalities, and reduced ejection fraction.[89]

ELECTROCUTION

ETIOLOGY. Accidental electrocution occurs most often in young animals from chewing an electrical cord.

PATHOPHYSIOLOGY. Cardiac injury can result from heat coagulation of myocardial protein, from disruption of electrophysiologic activity, and by prolonged arrhythmia-induced hypotension and relative myocardial ischemia during resuscitation. In dogs, subendocardial and subepicardial hemorrhage has been reported.[91] In electrocuted humans, widespread focal necrosis of the myocardium, SA and AV nodes, and the tunica media of the small coronary arteries was recorded.[93] The ECG may record sinus tachycardia, ventricular fibrillation, and S-T and T-wave changes.[92-94] Variably reversible echocardiographic abnormalities in humans include biventricular hypokinesis and left ventricular dyskinesia.[94]

Acute pulmonary edema following electrocution is common. It may represent a form of neurogenic pulmonary edema resulting from massive sympathetic activity, with venous and arterial constriction elevating pulmonary venous pressures.[91] Cardiac dysfunction may contribute to its development.[92]

CLINICAL SIGNS. Unconsciousness, tonic-clonic activity, oral burns, dyspnea (74 percent of dogs and 57 percent of cats), pulmonary edema, and emesis are reported. The mortality in dogs (n = 26) in one study was 39 percent, whereas none of seven cats succumbed.[91]

THERAPY. Animals suffering electrocution require management of pulmonary edema and accompanying myocardial dysfunction and arrhythmias. Furosemide, oxygen, corticosteroids, mechanical ventilatory support, inotropic support (digoxin, dobutamine, dopamine), and antiarrhythmic therapies (lidocaine and, ironically, electrical defibrillation) have all been employed.

SEPTIC SHOCK

ETIOLOGY. Bacteremia caused by gram-negative bacteria represents the most common cause. Both gram-positive and gram-negative canine septic shock have been associated with reduced mean arterial pressure, increased cardiac output, reduced ejection fraction, reduced ventricular compliance, and ventricular dilatation.[95]

PATHOPHYSIOLOGY. Septic shock produces myocardial depression characterized by LV dilatation, LV and RV functional depression and altered diastolic LV pressure-volume relationships.[95] Resultant cardiovascular derangements may be present after 1 to 4 days of shock. Although potentially reversible, they are important mortality factors.

Cardiovascular function in canine septic shock has received little clinical attention. However, experience and experimental data suggest that myocardial depression exists with forward, but not backward, heart failure. With coexistent heart disease, particularly the volume-overload state of aortic regurgitation due to vegetative endocarditis, left-sided congestive heart failure would likely ensue.

In hydrated human septic shock patients, cardiac output is normal or elevated, but this hyperdynamic state falls far short of meeting the needs of organs and cells under the conditions of septic shock.[95] Ventricular filling pressures do not rise with normal or supernormal cardiac output because systemic vascular resistance falls. Therefore, signs of congestion are rare in the absence of other cardiac disease (e.g., vegetative endocarditis). Late reductions in cardiac output are uncommon but highly correlated with death. They are associated with pulmonary wedge pressure elevation and reduced RV and LV stroke work. Some patients may die during the hyperdynamic stage of septic shock.

Endotoxin administered to humans and dogs produces similar cardiovascular changes observed in septic shock.[95] It is important to note that the same sequence of cardiovascular changes can be produced in dogs given *Staphylococcus aureus*, a microorganism without endotoxin, suggesting that cardiovascular injury during septic shock has a final common pathway (Fig. 33–8).[96] The cardiovascular effects of various known mediators of sepsis have been established in dogs and humans[95] (chapters 14, 15). Tumor necrosis factor released during septic shock may be an important myocardial depressant factor. It has been shown to have significant *in vitro* negative inotropic effects, whereas

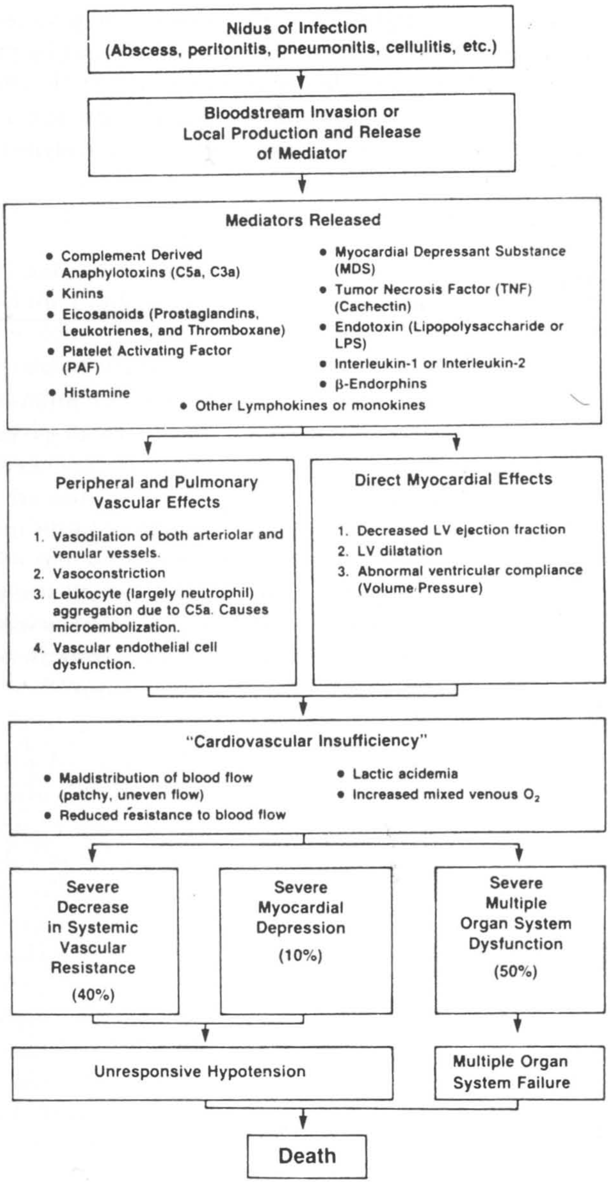


FIGURE 33–8

A schematic representation of the pathogenesis of human septic shock. (Reprinted with permission from Parker MM, Parillo JE: Septic shock. JAMA 250:3325, 1983.)

the interleukins and endotoxin do not. The role of myocardial depressant factor (MDF) has been established and pathophysiologic mechanisms postulated (Fig. 33–8).[96] Nearly half of septic shock patients have circulating MDF that is correlated with higher pulmonary artery wedge pressure, end-diastolic volume, and mortality; and with ventricular dysfunction. Activated complement component Ca reduces systemic vascular resistance but not myocardial function.[95]

Lastly, reduced myocardial β-receptor numbers and blunted β-agonist responsiveness have been observed in experimental animals and septic humans, respectively.[97] Elevated plasma catecholamine concentrations with β-receptor down regulation and/or direct antagonism of β-adrenergic receptors by endotoxin are thought to contribute to impaired responsiveness to endogenous catecholamines and, hence, myocardial depression.

CLINICAL SIGNS. Myocardial depression, ventricular dilatation, and arrhythmias are recognized in human and canine septic shock (see also Table 15–3).

THERAPY. Eradicating the source of sepsis with cardiovascular supportive measures constitutes the initial therapy. Shock doses of glucocorticoids (dexamethasone sodium phosphate, 4 mg/kg IV), appropriate antibiotics, and fluid therapy (crystalloids or colloids early in septic shock) are all indicated (see Table 15–4). Pressor agents may be necessary in cases that develop profound hypotension unresponsive to fluid therapy. Digoxin, dobutamine, and dopamine have been shown to be effective for inotropic support (see Figure 15–1). Prevention or correction of disseminated intravascular coagulation (DIC), oxygen therapy, and management of multiple organ system failure may all be indicated (chapters 14, 15).

IMMUNE-MEDIATED AND IMMUNODEFICIENCY DISEASES

Cardiovascular manifestations may accompany these disorders, as described in this section. Therapy, when indicated, is directed at treating serious arrhythmias (chapters 17, 18, 19) or heart failure (chapter 12).

SYSTEMIC LUPUS ERYTHEMATOSUS

This disease is well recognized in dogs, with females disproportionately affected.

PATHOPHYSIOLOGY. A clear or sanguineous proteinaceous effusion is associated with histologic lesions of fibrinoid degeneration, edema, and necrosis of pericardial connective tissue. Myocarditis, present in 40 percent of SLE patients, consists of fibrinoid necrosis of connective tissue and vessels, but rarely cardiac myocytes.[99] Endocardial lesions may occur. Verrucous valvular lesions (Libman-Sacks endocarditis) consist of degenerating valve tissue and fibrosis, but they are rarely severe enough to produce valvular insufficiency.

CLINICAL SIGNS. Signs are associated with antigen-antibody complexes and usually relate to thrombocytopenia, glomerulonephritis, immune complex joint disease, autoimmune hemolytic anemia, polymyositis, polyneuritis, and dermatitis. Myocarditis and pneumo-

nitis are less common.[98] Pericarditis is the most common cardiac affliction in humans, reported in up to 75 percent of systemic lupus erythematosus (SLE) autopsy cases. Physical examination findings include heart murmurs (due to valvular insufficiency and anemia) and cardiac gallop rhythms; muffled heart sounds or pericardial friction rubs; hypertension secondary to renal disease; and, occasionally, heart failure.[99, 100] Both systolic and diastolic dysfunction, as well as increased myocardial mass, have been associated with systemic SLE.[101] Pericarditis or pericardial effusion (39 percent), hypertension (22 percent), myocarditis (14 percent), congestive heart failure (10 percent), pulmonary hypertension (9 percent), and valvular heart disease (9 percent) were all noted.[100]

Compared with lesions in human SLE, little attention has been paid to the hearts of SLE-affected dogs. Reviews of reported canine and feline pericardial diseases reveal no mention of SLE or immune-mediated causes,[66, 67] although feline infectious peritonitis—with immune-mediated vasculitis as the underlying lesion—was the most common cause of pericardial disease in 66 cats.[66] One report of 30 SLE dogs describes ventricular arrhythmias in 2 and heart failure in 1 dog, although cardiac disorders were not confirmed by necropsy or echocardiography, and 2 of the dogs were breeds prone to dilated cardiomyopathy.[98] However, an antinuclear antibody (ANA)-positive, female Great Dane with ventricular tachycardia was reported to respond to steroid therapy, suggesting myocarditis, and an ANA-positive, 4-year-old female dachshund without a murmur died of heart failure.[98] Both dogs had other manifestations of SLE.

AMYLOIDOSIS

Certain types of amyloidosis are associated with myocardial infiltration and heart failure in humans.[102] Cardiac manifestations most commonly involve systolic dysfunction and failure. Some patients suffer from diastolic failure (restrictive cardiomyopathy), orthostatic hypotension, or ECG abnormalities.[102] Companion animals are relatively frequently afflicted with amyloidosis. Renal failure is the most common manifestation. Dogs and cats produce mainly reactive amyloid. Cardiac infiltration is not generally reported in dogs. Felines with amyloidosis may have mild-to-moderate cardiac amyloid deposition, but adverse clinical effects are not reported.[103]

IMMUNODEFICIENCY SYNDROMES

Dilated cardiomyopathy and heart failure have been described secondary to human acquired immunodeficiency syndrome (AIDS).[104] Systolic myocardial and congestive heart failure were documented with pericardial effusion and arrhythmias. However, although heart lesions have been described in cats infected with feline lentivirus (feline immunodeficiency virus), cardiac dysfunction and failure are not clinically significant manifestations.[105]

OBESITY

ETIOLOGY. Morbid obesity is present in 34 million adult Americans[27] and 20 to 44 percent of dogs in developed countries.[106] In humans, obesity is associated with an increased incidence of hypertension, but atherosclerosis is not a consistent association.[27] Little information is available regarding the cardiovascular effects of obesity in companion animals. A British study of more than 8000 dogs showed that gross obesity was associated with an increased incidence of cardiovascular disorders, whereas moderate obesity was not.[106]

PATHOPHYSIOLOGY. Cardiac changes are related primarily to volume overloading, with resultant eccentric hypertrophy and, ultimately, myocardial failure ("cardiomyopathy of overload"). An increase in blood volume proportional to the degree of obesity results in increased stroke volume. Ventricular filling pressures are normal at rest but rise dramatically with exercise. There is also an increased susceptibility to arrhythmias.[27] Hypertension adds an abnormally high afterload, further overloading the heart. Cor pulmonale ("pickwickian syndrome") is evident with the obesity-hypoventilation syndrome (i.e., obesity results in hypoventilation, causing alveolar hypoxia, pulmonary vasoconstriction, and pulmonary hypertension[10]) (see Fig. 33–2). Cor pulmonale is recognized in obese dogs with chronic obstructive pulmonary disease (COPD).[29] It is not clear whether obesity precipitates respiratory disease, which induces cor pulmonale, or whether obesity is primarily responsible for cardiac impairment. Most likely, obesity plays a role in aggravating or causing COPD, as well as inducing hypoventilation, each contributing to the development of cor pulmonale.

CLINICAL SIGNS. Historical and physical examination findings relate largely to chronic respiratory diseases and possibly cor pulmonale. Right heart enlargement may be evident radiographically, often reflected by ECG changes in dogs as P pulmonale (see Figure 6–14). Hypertension and arrhythmias can occur.

THERAPY. Weight reduction is beneficial in reversing volume overloading, hypertension, and hypertrophy, even after the onset of failure.[27]

NUTRITIONAL ABNORMALITIES

ETIOLOGY. Malnutrition complicates a variety of degenerative, neoplastic, and infectious diseases. Cardiac cachexia is a well-recognized phenomenon, frequently found in animals in heart failure (chapter 32).

PATHOPHYSIOLOGY. Consequences of malnutrition include fluid and electrolyte imbalances and generalized protein wasting, from which the heart is not spared. Cardiac manifestations include reduction in cardiac output, contractility, compliance, systolic pressure, and pulse pressure; cardiac atrophy with myofiber atrophy and interstitial edema; and increased sensitivity to cardiac glycosides.[27]

Specific nutritional deficiencies have been shown to cause or contribute to cardiac dysfunction in humans and animals (chapters 27, 28, 32). One prominent example is reversible dilated cardiomyopathy associated with inadequate dietary taurine.[107–110] Dilated cardiomyopathy in dogs has been associated with subnormal plasma and myocardial carnitine concentrations (chapters 27, 32).[9] Selenium deficiency produces human dilated cardiomyopathy (Keshan disease) in selenium-deficient areas in China but rarely in the United States.[111] A comparison of plasma selenium concentration in healthy cats and a limited number of cats with various types of cardiac disease showed no significant difference.[112] Severe thiamine deficiency (beriberi) produces a high-output form of cardiomyopathy, characterized by fulminant biventricular failure, murmur, and gallop.[24]

PREGNANCY

Normal human pregnancy is associated with increases in blood volume (40 to 50 percent increase), cardiac output (30 to 50 percent), stroke volume, heart rate, and velocity of circumferential fiber shortening; also, reductions in systemic blood pressure, systemic vascular resistance, and peripheral vascular resistance. Cardiac murmurs, probably related to reduction in packed cell volume and volume overload, are detected. The ECG may reveal an increased heart rate, arrhythmias, rate-related Q-T and P-R interval reduction, and changes in T wave and S-T segment.[113] Hypertension and peripartum cardiomyopathy may accompany human pregnancy.[114, 115] The importance of this syndrome in companion animals has not been demonstrated.

OTHER DISORDERS

Numerous other systemic and metabolic diseases can affect the heart and precipitate or contribute to heart failure. Tumors metastatic to the heart or great vessels may alter cardiac preload (restricting filling by venous or intracardiac obstruction, pericardial infiltration, or effusion), reduce systolic function (myocardial infiltration), or affect the hematopoietic system, as described earlier. Infectious diseases may also produce heart failure or other cardiac dysfunction. Trypanosomiasis, toxoplasmosis, borreliosis, feline infectious peritonitis, Rocky Mountain spotted fever, and parvovirus infection are examples of infectious diseases associated with cardiac manifestations in pets.[116] Toxins capable of producing cardiac disease and potential failure include alcohol, gossypol, doxorubicin, heavy metals, phenothiazines, hydrocarbons, catecholamines, arachnid stings, snake bites, pesticides, biotoxins, and others.[29, 102, 117] Gossypol intoxication has been associated with heart failure in two dogs who died after consuming meal containing gossypol cottonseed.[118] Lesions included right-sided heart failure (ascites), diminished LV function, ECG changes (biventricular and left atrial enlargement; idioventricular rhythm, and/or QT prolongation); and myocyte degeneration, with intra- and intercellular edema and minimal inflammation.

REFERENCES

1. Atkins CE. The role of noncardiac disease in the development and precipitation of heart failure. Vet Clin North Am 21:1035, 1991
2. Katz AM. Cardiomyopathy of overload. N Engl J Med 322:100, 1990
3. Braunwald E. Pathophysiology of heart failure. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 3rd ed. Philadelphia, WB Saunders, 1988, p 426
4. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 56:56, 1975
5. Lakatta EG. Starling's law of the heart is explained by an intimate interaction of muscle length and myofilament calcium activation. J Am Coll Cardiol 10:1157, 1987
6. Meerson FZ. The myocardium in hyperfunction, hypertrophy, and heart failure. Circ Res 25:1, 1969
7. Mirsky I, Pfeifer JM, Pfeifer MA, et al. The contractile state as the major determinant in the evolution of left ventricular dysfunction in the spontaneously hypertensive rat. Circ Res 53:767, 1983
8. Fifer MA, Borow KM, Colan SD, et al. Early diastolic left ventricular function in children and adults with aortic stenosis. J Am Coll Cardiol 5:1147, 1985
9. Bonagura JD, Keene BW. Therapy for heart failure. *In* Bonagura JD (ed): Kirk's Current Veterinary Therapy. Vol XII. Philadelphia, WB Saunders, 1995, p 780
10. McFadden ER Jr, Braunwald E. Cor pulmonale. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 3rd ed. Philadelphia, WB Saunders, 1988, p 1597
11. Enson Y, Giuntini C, Lewis ML, et al. The influence

of hydrogen ion concentration and hypoxia on the pulmonary circulation. J Clin Invest 43:1146, 1964
12. Snyder DW. Cardiac manifestations of noncardiac disease in the elderly. *In* Messerli FH (ed): Cardiovascular Disease in the Elderly. Boston, Martinus Nijhoff Publishing, 1988, p 263
13. Fox PR. Cor pulmonale. *In* Kirk RW (ed): Current Veterinary Therapy IX. Philadelphia, WB Saunders, 1986, p 313
14. Malik AB, Kidd BSL. Time course of pulmonary vascular response to hypoxia in dogs. Am J Physiol 224:1, 1973
15. Klinger JR, Hill NS. Right ventricular dysfunction in chronic obstructive pulmonary disease. Chest 99:715, 1991
16. Rawlings CA. Cardiopulmonary function in the dog with *Dirofilaria immitis* infection: During infection and after treatment. Am J Vet Res 41:319, 1980
17. Amis TC. Chronic bronchitis in dogs. *In* Kirk RW (ed): Current Veterinary Therapy. Vol IX. Philadelphia, WB Saunders, 1986, p 306
17a. Juan G, Calverley P, Talamo C, et al. Effect of carbon dioxide on diaphragmatic function in human beings. N Engl J Med 310:874, 1984
17b. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 333:817, 1995
18. Burns MG. Pulmonary thromboembolism. *In* Kirk RW (ed): Current Veterinary Therapy. Vol VII. Philadelphia, WB Saunders, 1983, p 257
19. Rosenow EC III, Osmundson PJ, Brown ML. Pulmonary embolism. Mayo Clin Proc 56:161, 1981
20. Fluckiger MA, Gomez J. Radiographic findings in dogs with spontaneous thrombosis or embolism. Vet Radiol 25:124, 1984
21. Atkins CE, Lehner CE, Beck KA, et al. Experimental respiratory decompression sickness in sheep. J Appl Physiol 65:1163, 1988
22. Suter PF. Peripheral vascular diseases. *In* Ettinger SJ (ed): Textbook of Veterinary Internal Medicine. 3rd ed. Philadelphia, WB Saunders, 1989, p 1185
23. Aiken SW, Jakovljevic A, Lantz GC, Blevins WE. Acquired arteriovenous fistula secondary to castration in a dog. J Am Vet Med Assoc 202:965, 1993
24. Grossman W, Braunwald E. High-cardiac output states. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 3rd ed. Philadelphia, WB Saunders, 1988, p 778
25. Calvert C. Congestive cardiomyopathy in Doberman pinscher dogs. J Am Vet Med Assoc 181:598, 1982
26. Panciera DL. M-mode echocardiographic and electrocardiographic findings before and after levothyroxine treatment in hypothyroid dogs; Abstract. J Vet Intern Med 7:115, 1993
27. Williams GH, Braunwald E. Endocrine and nutritional disorders and heart disease. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 3rd ed. Philadelphia, WB Saunders, 1988, p 1800
28. Buccino RA, Spann JF, Poole E, et al. Influence of the thyroid state on intrinsic contractile properties and the energy stores of the myocardium. J Clin Invest 46:1669, 1967
29. Fox PR, Nichols CER. Cardiac involvement in systemic disease. *In* Fox PR (ed): Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 565
30. Liu S, Tilley LP, Tappe JP, Fox PR. Clinical and pathologic findings in dogs with atherosclerosis: 21 cases (1970–1983). J Am Vet Med Assoc 189:227, 1986
31. Miller CW, Boone JA, Soderberg SA, et al. Echocardiographic assessment of cardiac function in beagles with experimentally produced hypothyroidism. J Ultrasound Med 3(suppl):157, 1984
32. Santos AD, Miller RP, Puthenpurakal KM, et al. Echocardiographic characterization of the reversible cardiomyopathy of hypothyroidism. Am J Med 68:675, 1980
32a. Broussard JD, Peterson ME, Fox PR. Changes in clinical and laboratory findings in cats with hyperthyroidism from 1983 to 1993. J Am Vet Med Assoc 206:302, 1995
32b. Peterson ME. Hyperthyroid diseases. *In* Ettinger SH, Feldman ED (eds): Textbook of Veterinary Internal Medicine. Philadelphia, WB Saunders, 1995, p 1446
33. Willard MD, Schall WD, McCaw DE, et al. Canine hypoadrenocorticism: Report of 37 cases and review of 39 previously reported cases. J Am Vet Med Assoc 180:59, 1982
34. Peterson ME, Greco DS, Orth DN. Primary hypoadrenocorticism in ten cats. J Vet Intern Med 3:55, 1989
35. Musselman EE. Endocrine cardiomyopathies. Proc Acad Vet Cardiol, 1990, p 18
35a. Peterson ME, Kintzer PP, Kass PH. Pretreatment clinical and laboratory findings in 225 dogs with hypoadrenocorticism. J Am Vet Med Assoc 208:85, 1996
36. Knowlton AI, Baer L. Cardiac failure in Addison's disease. Am J Med 74:829, 1984
37. Nelson RW, Feldman EC, Smith MC. Hyperadrenocorticism in cats: Seven cases (1978–1987). J Am Vet Med Assoc 193:245, 1988
38. Breitschwerdt EB, Meuten DJ, Greenfield CL, et al. Idiopathic hyperaldosteronism in a dog. J Am Vet Med Assoc 187:841, 1985
39. Eger CE, Robinson WF, Huxtable CRR. Primary aldosteronism (Conn's syndrome) in a cat: A case report and review of comparative aspects. J Small Anim Pract 24:293, 1983
40. Twedt DC, Wheeler SL. Pheochromocytoma in the dog. Vet Clin North Am 14:767, 1984
41. Bouyard H, Feeney DA, Caywood DD. Pheochromocytoma in dogs: 13 cases (1980–1985). J Am Vet Med Assoc 191:1620, 1987
42. Feldman EC, Nelson RW. Growth Hormone in Canine and Feline Endocrinology and Reproduction. Philadelphia, WB Saunders, 1987, p 29
43. Peterson ME. Unusual endocrine disease in the cat. Proc Am Coll Vet Intern Med, 1988, p 6
44. Kittleson MD, Pion PD, Lothrop CD, et al. Hypersomatotropism in a cat presenting with hypertrophic cardiomyopathy (HCM) and insulin resistance but without diabetes mellitus (DM); Abstract. Proc Am Coll Vet Intern Med, 1989, p 1038
45. Kittleson MD. Relationship between hypertrophic cardiomyopathy and hypersomatotropism in the cat. 8th Annual Forum, American College of Veterinary Internal Medicine, 1990
46. Atkins CE, Gallo AM, Kurzman I, Cowen P. Risk factors, clinical signs, and survival in cats with a clinical diagnosis of idiopathic hypertrophic cardiomyopathy: 74 cases (1985–1989). J Am Vet Med Assoc 201:613, 1992
47. Fein FS, Sonnenblick EH. Diabetic cardiomyopathy. Prog Cardiovasc Dis 27:255, 1985
48. Atkins CE, Engerman RL, Kern TS. Diabetic cardiomyopathy. Proc Am Coll Vet Intern Med 2:9, 1988
49. Pierce GN, Blamish RE, Naranjan SD. Diabetic Cardiomyopathy: Present Status and Future Directions. Boca Raton, FL, CRC Press, 1988, p 225
50. Follansbee WP, Schulman DS, Curtiss EI, et al. Diastolic function in diabetes: Results from the epidemiology

of diabetic complications study; Abstract. Circulation 80:76, 1989
51. Follansbee WP, Curtiss EI, Schulman DS, et al. Diabetic cardiomyopathy: Final results of diabetes complications study; Abstract. Circulation 80:206, 1989
52. Atkins CE, Keene BW, Engerman RL. Inability to detect parasympathetic autonomic neuropathy in experimental canine diabetes mellitus in an electrocardiographic study. Diabetes Res 11:39, 1989
53. Braund KG, Steiss JE. Distal neuropathy in spontaneous diabetes mellitus in the dog. Acta Neuropathol 57:263, 1982
54. Kramek BA, Moise NS, Cooper B, et al. Neuropathy associated with diabetes mellitus in the cat. J Am Vet Med Assoc 184:42, 1984
55. Mostafa IA. A case of glycogenic cardiomegaly in a dog. Acta Vet Scand 11:197, 1970
56. Walvoort HC, van Nes JJ, Stokhof AA, et al. Canine glycogen storage disease type II: A clinical study of four affected Lapland dogs. J Am Anim Hosp Assoc 20:279, 1984
57. Connor TB, Rosen BL, Blaustein MP, et al. Hypocalcemia precipitating congestive heart failure. N Engl J Med 307:869, 1982
58. Ginsburg R, Esserman BA, Bristow MR. Myocardial performance and extracellular ionized calcium in a severely failing human heart. Ann Intern Med 98:603, 1983
59. Lang RM, Fellner SK, Neumann A, et al. Left ventricular contractility varies directly with blood ionized calcium. Ann Intern Med 108:524, 1988
60. Fitzovich DE, Hamaguchi M, Tull WB, Young BR. Chronic hypokalemia and the left ventricular responses to epinephrine and preload. J Am Coll Cardiol 18:1105, 1991
61. Dyckner T, Wester PO. Potassium/magnesium depletion in patients with cardiovascular disease. Am J Med 82(3A):11, 1987
62. Iseri LT, French JH. Magnesium: Nature's physiologic calcium blocker. Am Heart J 108:188, 1984
63. Hollifield JW. Magnesium depletion, diuretics, and arrhythmias. Am J Med 82(3A):30, 1987
64. Pastan SO, Braunwald E. Renal disorders and heart disease. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB Saunders, 1988, p 1828
65. Madewell BR, Norrdin RW. Renal failure associated with pericardial effusion in a dog. J Am Vet Med Assoc 167:1091, 1975
66. Rush JE, Keene BW, Fox PR. Pericardial disease in the cat: A retrospective evaluation of 66 cases. J Am Anim Hosp Assoc 26:39, 1990
67. Berg RJ, Wingfield W. Pericardial effusion in the dog: A review of 42 cases. J Am Anim Hosp Assoc 20:721, 1984
68. Halmagyi DF, Karis JH, Stenning FG, et al. Pulmonary hypertension in acute hemorrhagic pancreatitis. Surgery 76:637, 1974
69. Strombeck DR. The pancreas. *In* Small Animal Gastroenterology. Davis, CA, Stonegate Publishing, 1979, p 301
70. Muir WW. Gastric dilatation-volvulus in the dog, with emphasis on cardiac arrhythmias. J Am Vet Med Assoc 180:739, 1982
71. Muir WW, Weisbrode SE. Myocardial ischemia in dogs with gastric dilatation-volvulus. J Am Vet Med Assoc 181:363, 1983
72. Horne WA, Gilmore DR, Dietze AE, et al. Effects of gastric distention-volvulus on coronary blood flow and myocardial oxygen consumption in the dog. Am J Vet Res 46:98, 1985
73. Orton EC, Muir WW. Hemodynamics during experimental gastric dilatation-volvulus in dogs. Am J Vet Res 44:1512, 1983
74. Orton EC, Muir WW. Isovolumetric indices and humoral cardioactive substance assay during clinical and experimentally induced gastric dilatation-volvulus in dogs. Am J Vet Res 44:1516, 1983
75. King JM, Roth L, Haschek WM. Myocardial necrosis secondary to neural lesions in domestic animals. J Am Vet Med Assoc 180:144, 1982
76. Rosenthal DS, Braunwald E. Hematological-oncological disorders and heart disease. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB Saunders, 1988, p 1734
77. Yaphe W, Giovengo S, Moise NS. Severe cardiomegaly secondary to anemia in a kitten. J Am Vet Med Assoc 202:961, 1993
78. Hohenhaus AE. Syndromes of hyperglobulinemia: Diagnosis and therapy. *In* Bonagura JD (ed): Kirk's Current Veterinary Therapy XII. Philadelphia, WB Saunders, 1994, p 523
79. Hurvitz AI, Haskins SC, Fisher CA. Macroglobulinemia with hyperviscosity syndrome in a dog. J Am Vet Med Assoc 157:455, 1970
80. MacEwen EG, Hurvitz AI, Hayes A. Hyperviscosity syndrome associated with lymphocytic leukemia in three dogs. J Am Vet Med Assoc 170:1309, 1977
81. Shull RM, Osborne CA, Barrett RE, et al. Serum hyperviscosity syndrome associated with IgA multiple myeloma in two dogs. J Am Anim Hosp Assoc 14:58, 1978
82. Mejia EB, Carman S, Lumsden JH. Macroglobulinemia in a dog. Can Vet J 20:28, 1979
83. Pruzanski W, Watt JG. Serum viscosity and hyperviscosity syndrome in IgG multiple myeloma: Report of 10 patients and a review of the literature. Ann Intern Med 77:853, 1972
84. Kyle RA. Multiple myeloma; review of 869 cases. Mayo Clin Proc 50:29, 1975
85. McBride W, Jackman JD, Gammon RS, et al. High-output cardiac failure in patients with multiple myeloma. N Engl J Med 319:1651, 1988
86. Johnston KE. Pathophysiology of heat stroke. Compend Contin Educ Pract Vet 4:141, 1982
87. Zaher D, Moses A, Weiss AT. Evidence of prolonged myocardial dysfunction in heat stroke. Chest 95:1089, 1989
88. El-Kassimi FA, Al-Mashhadani S, Abdullah AK, et al. Adult respiratory distress syndrome and disseminated intravascular coagulation complicating heat stroke. Chest 90:571, 1986
89. Maaravi Y, Weiss AT. The effect of prolonged hypothermia on cardiac function in a young patient with accidental hypothermia. Chest 98:1019, 1990
90. Goldberg LI. Effects of hypothermia on contractility of the intact dog heart. Am J Physiol 94:92, 1958
91. Kolata RJ, Burrows CF. The clinical features of injury by chewing electrical cords in dogs and cats. J Am Anim Hosp Assoc 7:219, 1981
92. Schein RMH, Kett DH, De Marchena EJ, Sprung CL. Pulmonary edema associated with electrical injury. Chest 97:1248, 1990
93. James TN, Riddick L, Embry JH. Cardiac abnormalities demonstrated postmortem in four cases of accidental electrocution and their potential significance relative to nonfatal electrical injuries of the heart. Am Heart J 120:143, 1990

94. Homma S, Gillam LD, Weyman AE. Echocardiographic observations in survivors of acute electrical injury. Chest 97:103, 1990
95. Cunnion RE, Parrillo JE. Myocardial dysfunction in sepsis—Recent insights. Chest 95:941, 1989
96. Parker MM, Parrillo JE. Septic shock. Hemodynamics and pathogenesis. J Am Med Assoc 250:3325, 1983
97. Nasraway SA, Rackow EC, Astiz ME, et al. Inotropic response to digoxin and dopamine in patients with severe sepsis, cardiac failure, and systemic hypoperfusion. Chest 95:612, 1989
98. Drazner FH. Systemic lupus erythematosus in the dog. Compend Contin Educ Pract Vet 2:243, 1980
99. Stollerman GH. Rheumatic and heritable connective diseases of the cardiovascular system. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 3rd ed. Philadelphia, WB Saunders, 1988, p 1706
100. Badui E, Garcia-Rubi D, Jimenez J, et al. Cardiovascular manifestations in systemic lupus erythematosus. Prospective study of 100 patients. Angiology 36:431, 1985
101. Crozier IG, Li E, Milne MJ, Nicholls MG. Cardiac involvement in systemic lupus erythematosus detected by echocardiography. Am J Cardiol 65:1145, 1990
102. Wynne J, Braunwald E. The cardiomyopathies and myocarditides. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 3rd ed. Philadelphia, WB Saunders, 1988, p 1410
103. DiBartola SP, Benson MD. The pathogenesis of reactive systemic amyloidosis. J Am Coll Vet Intern Med 3:31, 1989
104. Cohen IS, Anderson DW, Virmani R, et al. Congestive cardiomyopathy in association with acquired immunodeficiency syndrome. N Engl J Med 315:628, 1986
105. Pederson NC, Yamamoto JK, Ishida T, et al. Feline immunodeficiency virus infection. Vet Immunol Immunopathol 21:111, 1989
106. Edney ATB, Smith PM. Study of obesity in dogs visiting veterinary practices in the United Kingdom. Vet Rec 118:391, 1986
107. Pion PD, Kittleson MD, Rogers QR, et al. Myocardial failure in cats associated with low plasma taurine: A reversible cardiomyopathy. Science 764, 1987
108. Atkins C, Snyder P: Cardiomyopathy. *In* Allen DG (ed): Small Animal Medicine. Philadelphia, JB Lippincott, 1991, p 269
109. Sisson D, Knight DH, Helinski C, et al. Plasma taurine concentrations and m-mode echocardiographic measures in healthy cats and cats with dilated cardiomyopathy. J Vet Intern Med 5:232, 1991
110. Pion PD, Kittleson MD, Thomas WP, et al. Response in cats with dilated cardiomyopathy to taurine supplementation. J Am Vet Med Assoc 201:275, 1992
111. Johnson RA, Baker SS, Fallon JT. An accidental case of cardiomyopathy and selenium deficiency. N Engl J Med 304:1210, 1981
112. Fox PR, Trautwein EA, Hayes KC, et al. Comparison of taurine, α-tocopherol, retinol, selenium, and total triglycerides and cholesterol concentrations in cats with cardiac disease and in healthy cats. Am J Vet Res 54:563, 1993
113. Perloff JK. Pregnancy and cardiovascular disease. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 3rd ed. Philadelphia, WB Saunders, 1988, p 1848
114. Homans DC. Peripartum cardiomyopathy. N Engl J Med 312:1433, 1985
115. Sandusky GE, Cho D. Congestive cardiomyopathy in a dog associated with pregnancy. Cornell Vet 74:60, 1984
116. Calvert CA, Dow SW. Cardiovascular infections. *In* Greene CE (ed): Infectious Diseases of the Dog and Cat. Philadelphia, WB Saunders, 1990, p 97
117. Murphy MJ. Toxin exposure in dogs and cats: Pesticides and biotoxins. J Am Vet Med Assoc 205:414, 1994
118. Patton CS, Legendre AM, Gompf RE, et al. Heart failure caused by gossypol poisoning in two dogs. J Am Vet Med Assoc 187:625, 1985

34

Hyperthyroidism and Other High Output States

PHILIP R. FOX
JOHN D. BROUSSARD
MARK E. PETERSON

CARDIAC RESPONSE IN HYPERMETABOLIC AND HYPERKINETIC STATES

Cardiac output may be increased by systemic and metabolic conditions that chronically elevate venous return. These include disorders that lower peripheral vascular resistance owing to increased tissue metabolism and oxygen demand (fever, thyrotoxicosis, or pregnancy), or that result in hyperkinetic states (anemia, systemic arteriovenous fistulas).[1-3] Cardiac output, the quantity of blood pumped by the heart through the systemic circulation per unit of time, is determined by the product of stroke volume and heart rate. Stroke volume is influenced by venous return (preload), afterload, and myocardial contractility (chapters 3, 11).

High-output heart failure represents a condition in which cardiac output is markedly elevated before the development of heart failure and remains high afterward. The normal heart is capable of compensating for increased cardiac output on a long-term basis by cardiac dilation (in response to a larger blood volume) and hypertrophy.[1,2] However, congestive heart failure may result when abnormal metabolic conditions or hyperkinetic states are imposed on a heart that has already developed intrinsic myocardial dysfunction. In veterinary medicine, the most common condition leading to high-output heart failure is feline hyperthyroidism. Less common causes include anemia and arteriovenous shunts.

Cardiovascular adaptation to an abnormal workload depends on the state of myocardial function and the magnitude of systemic burden. Moreover, the quicker the high-output state develops, the more likely it is that heart failure will ensue.[1]

HYPERTHYROIDISM

Hyperthyroidism (thyrotoxicosis) is a multisystem disorder resulting from excessive circulating serum concentrations of thyroxine (T_4) and triiodothyronine (T_3). Naturally occurring hyperthyroidism is the most commonly

diagnosed endocrinopathy of cats, although it is rare in dogs.[4] Functional thyroid adenomatous hyperplasia (or adenoma) involving one or both thyroid lobes is the most common etiology; thyroid carcinoma is rare in cats but is generally the etiology in dogs.[4–7] The prevalence of feline hyperthyroidism at The Animal Medical Center is approximately 1 to 2 percent of all cats examined.

Excessive circulating thyroid hormone may cause reversible cardiomyopathy in an otherwise healthy heart[8, 9] or cause compensated heart failure to become decompensated.[1, 2] Hyperthyroidism should always be considered in any cat 6 years of age or older that exhibits clinical evidence of cardiac disease.

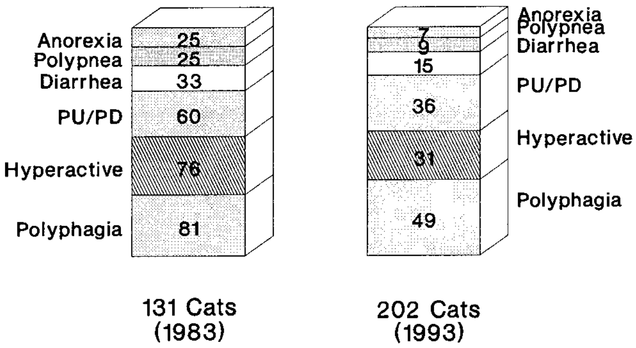


FIGURE 34–1

A comparison of the most common clinical signs recorded from two different populations of hyperthyroid cats studied approximately 10 years apart.[18] Chi square analysis applied to the comparative percentages indicated that the clinical signs of anorexia, polypnea, diarrhea, polyuria/polydypsia (PU/PD), hyperactivity, and polyphagia were significantly less common in the 1993 vs. 1983 populations ($P < .001$).

PATHOPHYSIOLOGY

Hyperthyroidism causes multiple physiologic derangements. It increases metabolic rate and tissue oxygen consumption and decreases peripheral vascular resistance. Compensatory cardiac remodeling results from changes in myocardial protein synthesis and degradation that favor hypertrophy. Direct actions of thyroid hormones on the heart muscle (directly influencing expression of myosin heavy chain genes), as well as T_4 and T_3 interactions with the sympathetic nervous system, stimulate cardiac hypertrophy and increase plasma volume and systemic blood pressure, cardiac output, cardiac filling pressures, heart rate, and contractility.[1–3, 9–13]

The most important factors in the development of heart failure are the chronicity and rate of development of the thyrotoxic state and the presence and severity of underlying cardiac disease.[9, 10] In long-standing cases, the increase in cardiac work may augment cardiac hypertrophy or precipitate congestive heart failure.[3, 9, 14–17] In humans, left ventricular ejection fraction has been shown to be elevated at rest but impaired during exercise.[14]

DIAGNOSIS

SIGNALMENT AND HISTORY

Hyperthyroidism occurs in middle-aged to old cats. The reported range is 4 to 22 years (median age, approximately 13 years). In general, hyperthyroidism is uncommon in cats less than 6 years of age. There is no breed or sex predilection.[4, 7, 18]

Because of the multisystemic effects of hyperthyroidism, most affected cats have clinical signs attributable to many organ systems. The most common abnormalities include weight loss, polyphagia, vomiting, polyuria, polydipsia, and increased activity (Fig. 34–1).[4, 7, 18] Approximately 5 percent of affected cats display a syndrome similar to apathetic hyperthyroidism in humans, characterized by profound depression, weakness, and anorexia.[4, 7]

PHYSICAL EXAMINATION FINDINGS

Most affected cats exhibit progressive weight loss and hyperactivity. They can be difficult to handle and become easily tachypneic and dyspneic when stressed. Some have unkempt hair coats with excessive shedding and matting. Since feline thyroid lobes are loosely attached to the trachea, enlarged lobes frequently can be palpated as they descend ventrally from their normal location adjacent to the larynx.[4, 7, 18] When thyroid glands are not palpable, affected lobe(s) may have descended into the thoracic cavity.[19]

In a series of 202 hyperthyroid cats, thoracic auscultation revealed soft-to-moderate systolic murmurs of mitral and tricuspid regurgitation (54%), tachycardia (42%), and gallop rhythms (15%).[18] Cats with decompensated heart failure may be dyspneic, have abnormal respiratory crackles if pulmonary edema is present, have muffled heart and lung sounds if pleural effusion has occurred, or have palpable femoral arterial pulse deficits. A hyperkinetic, rapid femoral arterial pulse and a prominent left apical precordial beat are generally detectable.

ELECTROCARDIOGRAPHY

A wide variety of electrocardiographic (ECG) changes have been described with feline hyperthyroidism.[4, 7, 16–18, 20–26] Descriptive characteristics of the P-QRS-T complex in feline hyperthyroidism are listed in Table 34–1. The frequency of ECG abnormalities in 119 hyperthyroid cats indicated sinus tachycardia (heart rate ≥ 240 beats/min) in 38 percent, increased R-wave amplitude in lead II (≥ 0.9 mV) in 8 percent,

TABLE 34–1
Descriptive Characteristics of the P-QRS-T Complex in Hyperthyroid Cats

ECG Mensural	Mean	SD	Median	Number
P-wave amplitude (mV)	0.14	0.06	0.1	118
P-wave width (msec)	31	6.0	30	118
PR interval (msec)	70	11.6	70	116
R-wave amplitude (mV)	0.4	0.35	0.3	119
QRS duration (msec)	37	11	35	117
QT interval (msec)	154	27.5	155	106
Heart rate	229	38.2	230	119

various atrial (3%) and ventricular (4%) arrhythmias, and intraventricular conduction disturbances (Table 34–2; Fig. 34–2).

The ability of β-adrenergic blockers (propranolol or atenolol) to decrease heart rate in the face of elevated circulating thyroid hormone levels provides indirect evidence for the contribution of the sympathetic nervous system to these arrhythmias.[3, 10] Tachycardia, increased R-wave amplitude, and many arrhythmias often resolve after euthyroidism has been re-established (Figs. 34–2, 34–3).[4, 7, 9, 15, 18, 21]

RADIOGRAPHY

Thoracic radiographs commonly demonstrate cardiomegaly, especially of the left atrium and ventricle. Congestive heart failure, manifested as pulmonary edema, pleural effusion, or both, may be evident in a small percentage of hyperthyroid cats (see later section on epidemiologic changes).[7, 16–18, 20–22, 24] Many of these radiographic abnormalities are partially or completely reversible after euthyroidism has been re-established (Fig. 34–4).

ECHOCARDIOGRAPHY

Echocardiographic abnormalities associated with hyperthyroidism include left ventricular hypertrophy, left

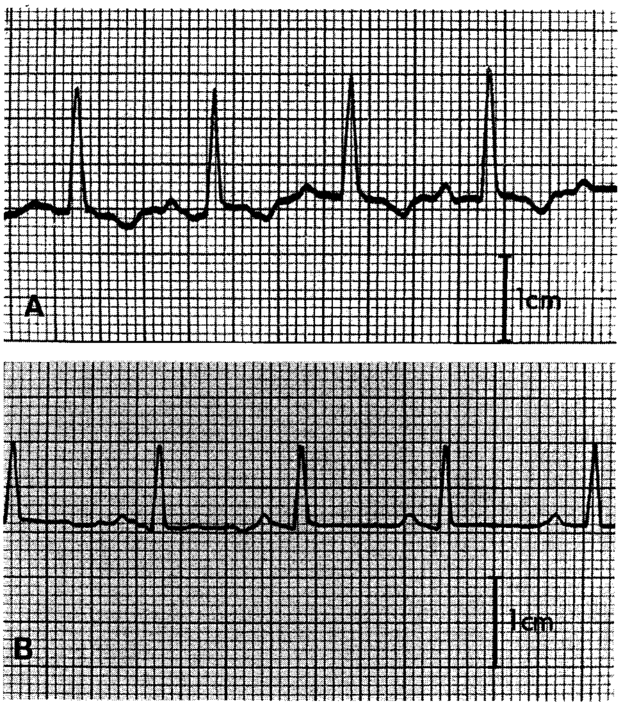


FIGURE 34–2

Lead II electrocardiograms of a 9-year-old domestic shorthair cat with hyperthyroidism before (A) and 3 months after (B) thyroidectomy. (A) Left ventricular enlargement is indicated by tall R waves (1.35 mV) and widened QRS complexes (45 msec). First-degree AV block (P-R interval, 95 msec) is also present. Heart rate is 200 beats/min. (B) Three months after thyroidectomy: R-wave amplitude is reduced to 0.9 mV; QRS width and P-R interval have reverted to normal. Paper speed, 50 mm/sec; 1 cm = 1 mV.

atrial and ventricular dilation, and hypercontractility (manifested by increased shortening fraction and velocity of circumferential fiber shortening).[15–17, 21, 22] Findings may mimic those present with primary myocardial disease (hypertrophic cardiomyopathy).[23] Many cardiac changes resolve or revert toward normal after re-establishment of euthyroidism. This indicates the reversible nature of thyrotoxic heart disease.[9, 11, 12, 15] Although uncommon, a dilatative type of cardiomyopathy has been reported, with hyperthyroidism evidenced

TABLE 34–2
Comparison of Salient Electrocardiographic Findings in Hyperthyroid Cats Evaluated in 1983 vs. 1993

ECG Finding	1983 Population (n = 131)	1993 Population (n = 119)	P
Sinus tachycardia	87 (66%)	41 (34%)	0.001
R-wave amplitude >0.9 mV (lead II)	38 (29%)	9 (8%)	0.001
Atrial extrasystoles	9 (7%)	2 (2%)	NS
Atrial tachycardia	1 (1%)	1 (1%)	NS
Ventricular extrasystoles	3 (2%)	0	NS
Ventricular tachycardia	1 (1%)	0	NS
First-degree AV block	2 (2%)	2 (2%)	NS
LAFB	8 (6%)	9 (8%)	NS
RBBB	2 (2%)	11 (9%)	0.008
LBBB	0	2 (2%)	NS

AV, atrioventricular; LAFB, left anterior fascicular block; RBBB, right bundle branch block; LBBB, left bundle branch block; NS, not significant.

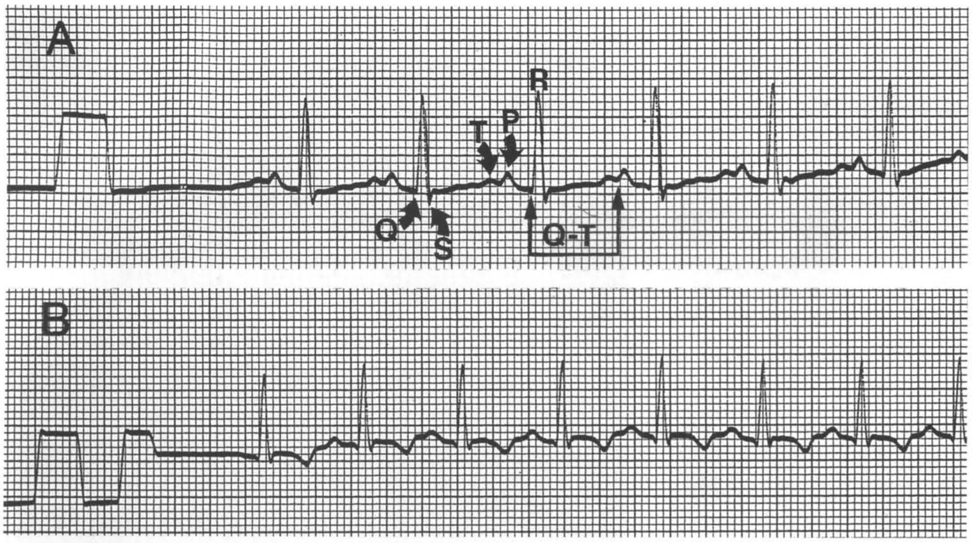


FIGURE 34–3

Lead II electrocardiograms of a 14-year-old domestic shorthair cat. (A) ECG recorded 24 hours post bilateral thyroidectomy during a hypocalcemic crisis (Ca^{++}, 2.8 mg/dl). The Q-T interval is abnormally prolonged (220 msec); R wave height is 1.2 mV, indicating left ventricular enlargement. (B) ECG recorded after medical therapy corrected the serum calcium deficit. The Q-T interval is normal (170 mV). Paper speed, 50 mm/sec; 1 cm = 1 mV.

by reduced myocardial contractility, marked ventricular dilation, and congestive heart failure.

CLINICAL PATHOLOGY

Screening laboratory tests, including a complete blood count, serum biochemical profile, and urinalysis, should be performed on all cats suspected of having hyperthyroidism. This data base assists the diagnosis and may reveal other disorders. Mature leukocytosis, eosinopenia (stress response), and increased packed cell volume occur commonly. From a series of 202 hyperthyroid cats, there was elevated serum alanine aminotransferase (83%), aspartate aminotransferase (43%), alkaline phosphatase (58%), and lactic dehydrogenase (58%).[18] These abnormalities generally normalize soon after successful treatment of hyperthyroidism.

THYROID FUNCTION TESTS. Baseline serum T_3 and T_4 concentrations are elevated above the reference range in most cats with hyperthyroidism.[4, 7, 25] Determination of serum T_4 is of greatest diagnostic value. Approximately 25 percent of cats with elevated serum T_4 concentrations have serum T_3 concentrations within the reference range.[7, 18]

A small number of hyperthyroid cats have serum T_3 and T_4 concentrations that are within the normal to high-normal range. This clinical condition, termed occult hyperthyroidism, is reported in from 2 to 10 percent of hyperthyroid cats.[18, 19, 25] Possible explanations

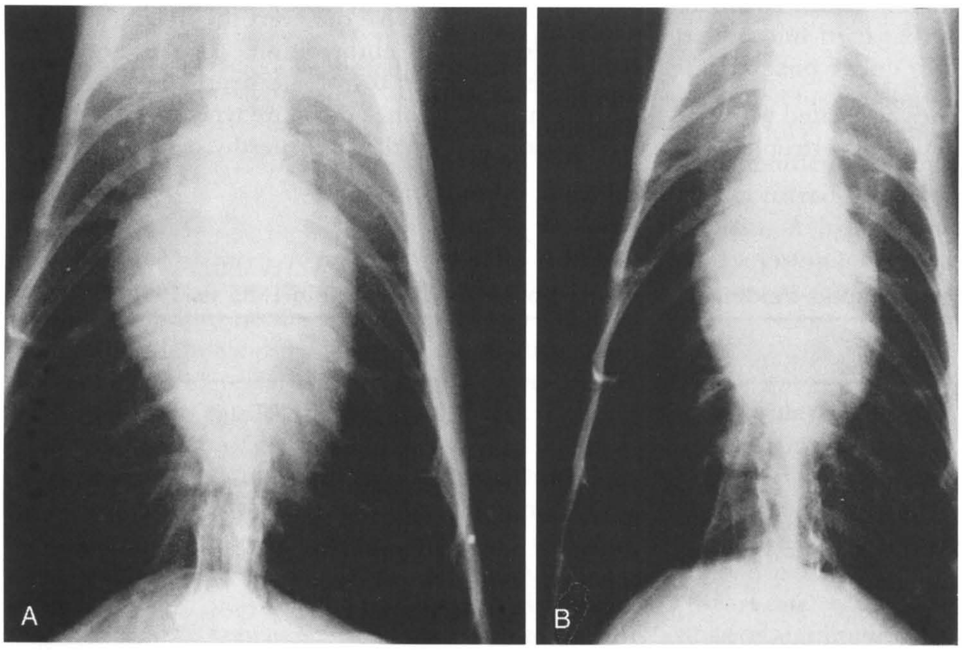


FIGURE 34–4

Ventrodorsal radiographs of an adult domestic shorthair cat with a unilateral thyroid gland adenoma. (A) Pretreatment radiograph shows biatrial and left ventricular enlargement. (B) One month after thyroidectomy, cardiomegaly is notably reduced.

include (1) suppression of high serum T_4 and T_3 concentrations into the normal range because of concurrent nonthyroidal illness,[27] and (2) fluctuation of T_4 and T_3 in and out of the normal range.[28] When one suspects mild hyperthyroidism but the serum T_4 concentration is not high, the first step is to rule out nonthyroidal illness and repeat the basal T_4 measurement in 1 to 2 weeks. If the result is again in the normal to high-normal range, provocative testing with a T_3 suppression test or thyrotropin-releasing hormone (TRH) stimulation test is recommended.[28, 29] Alternatively, determination of basal free T_4 concentrations (i.e., that portion of T_4 not bound to plasma proteins) may be helpful in diagnosis of occult hyperthyroidism. This is because most cats with high-normal total T_4 concentrations will have high serum-free T_4 levels.[26a]

RADIONUCLIDE THYROID IMAGING

Thyroid imaging (scanning) delineates functioning thyroid tissue and is a useful adjunct for diagnosing hyperthyroidism: (1) It determines the extent of thyroid gland involvement and detects possible metastatic or ectopic thyroid tissue; (2) it determines whether one or both thyroid lobes are involved and aids in surgical planning; (3) it will identify and localize a thyroid lobe that has descended into the thoracic cavity, which cannot be palpated; and (4) it detects metastasis of a functional thyroid adenocarcinoma (Fig. 34–5).[4, 30] Pertechnetate (^{99m}Tc) is the radionuclide of choice because of more rapid uptake and a shorter half-life.

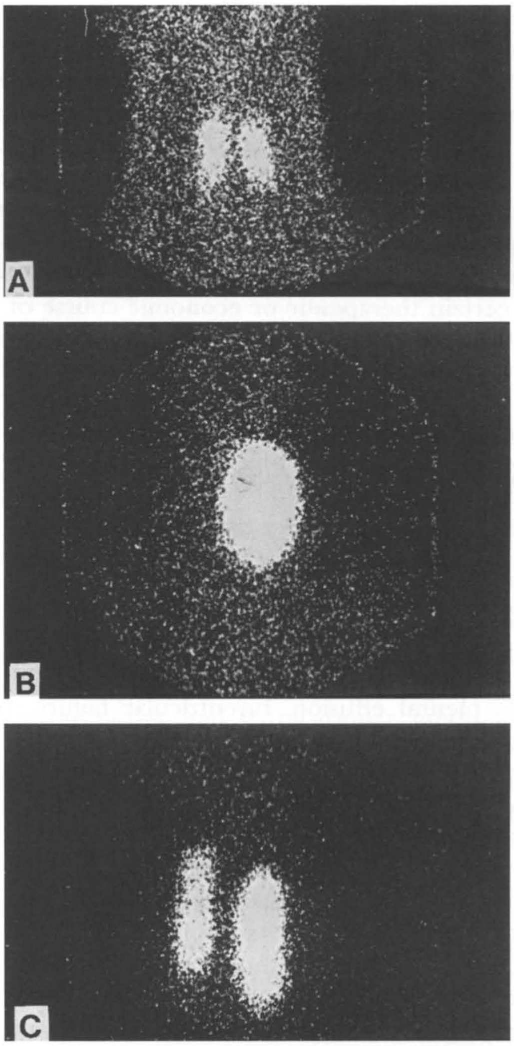


FIGURE 34–5

Sodium pertechnetate thyroid scans of (A) a clinically normal cat, (B) a hyperthyroid cat with adenoma (adenomatous hyperplasia) of one thyroid lobe, and (C) a hyperthyroid cat with bilateral thyroid gland adenomas. (A) Both thyroid lobes are symmetric in position and size, with uniform distribution of radioactivity throughout the gland. (B) The adenomatous gland is greatly enlarged and descends toward the thoracic inlet; the uninvolved right lobe is not visualized. (C) Both lobes are abnormally enlarged and approximately similar in size and position. (From Peterson ME, Kintzer PP, Cavanagh PG, et al: Feline hyperthyroidism: Pretreatment clinical and laboratory evaluation of 131 cases. J Am Vet Med Assoc 183:103, 1983.)

EPIDEMIOLOGIC CHANGES IN FELINE HYPERTHYROIDISM

The current prevalence and severity of thyrotoxic cardiovascular manifestations appear to be lower than reported in the earlier literature. When populations of hyperthyroid cats studied 10 years apart were contrasted (i.e., 202 cats examined from 1992 to 1993 compared with 131 cats diagnosed from 1979 to 1983), changes in clinical abnormalities were recorded. The prevalence of sinus tachycardia and high R-wave voltage (lead II) was lower in the 1993 population than the 1983 population. Regarding radiographic changes, no significant differences were recorded between populations in the number of cats with radiographic mild, moderate, or severe cardiomegaly. However, the percentage of cats in which radiographs were deemed clinically necessary was 20 percent of the 1993 population compared with 62 percent in 1983. Moreover, radiographic evidence of congestive heart failure was significantly less (8%) in the 1993 population compared with hyperthyroid cats studied in 1983 (29%). In addition, the prevalence of many associated clinical signs, physical examination findings, and laboratory abnormalities has decreased significantly when comparing populations (see Fig. 34–1).[18, 20] This is undoubtedly due to earlier recognition and therapy.

THERAPY OF HYPERTHYROIDISM

Feline hyperthyroidism can be treated by three different methods: (1) chronic oral administration of an

antithyroid drug, (2) surgical thyroidectomy of the affected lobe or lobes, or (3) radioactive iodine (^{131}I). Each has advantages and disadvantages, and several factors must be weighed in choosing the most appropriate therapy. Coexisting cardiovascular disease or other major disorders (e.g., renal failure) may influence the selected therapy, as do the availability of an experienced surgeon, a referral center for nuclear imaging and treatment, and the owner's desire to follow a certain therapeutic or economic course of therapy. Only thyroidectomy or radioactive iodine is curative.[4, 31]

TREATMENT OF CONGESTIVE HEART FAILURE OR TACHYRHYTHMIA

Long-standing thyrotoxicosis causes cardiovascular changes, most notably a reversible, secondary hypertrophic cardiomyopathy.[9] Heart failure associated with hyperthyroidism may be manifested as pulmonary edema, pleural effusion, biventricular failure, or arrhythmias.

Therapy is individualized based upon the presence and severity of secondary heart disease. Treatment to re-establish the euthyroid state promptly may significantly reduce, if not eliminate, heart failure and associated arrhythmias. Methimazole is usually chosen (5 to 15 mg divided bid to tid) as the first antithyroid drug of choice. Therapeutic thoracocentesis may be required if pleural effusion and associated dyspnea are severe. If pulmonary edema or effusion is present, furosemide should be administered (1 mg/kg bid to tid initially, then sid to bid). Generally, resolution of extracardiac signs (edema, effusion, and tachycardia) occurs within 2 to 7 days after methimazole and furosemide therapy is initiated. Beta-adrenergic receptor blocking drugs (propranolol, 2.5 to 5 mg bid to tid; atenolol, 6.25 mg sid) are administered only if severe tachyarrhythmias contribute to the heart failure state, but they are not otherwise given. If systolic dysfunction (myocardial failure) is revealed by echocardiography, β-blocking drugs are not given due to their negative inotropic effects. Very occasionally, digoxin may be useful (0.031 mg every 24 to 48 hours) for treatment of severe right-sided heart failure, myocardial failure, or atrial tachycardia, but it is not indicated in routine heart failure management.[4, 18, 21]

Once heart failure is controlled, definitive treatment of hyperthyroidism by surgical thyroidectomy or radioactive iodine therapy is performed. Cats that are unable to undergo surgery or radiotherapy may be maintained indefinitely on antithyroid drugs with periodic monitoring. Furosemide and other cardiac drugs administered for congestive heart failure are usually discontinued after hyperthyroidism is resolved.[4]

CHRONIC ORAL ANTITHYROID DRUGS

Methimazole (Tapazole) and propylthiouracil (PTU) are the two thionamide antithyroid drugs available in the United States. They lower serum T_4 and T_3 concentrations by inhibiting thyroid hormone synthesis without destroying thyroid tissue.

Long-term antithyroid drug treatment avoids the potential complication of hypothyroidism and postsurgical hypoparathyroidism. In addition, antithyroid drug therapy requires no advanced skills, training, or special licensing and is a practical treatment choice for most practitioners. Some systemic side effects are possible, however, and certain clients cannot tolerate long-term medication.

PROPYLTHIOURACIL (PTU). Although both methimazole and PTU are effective in decreasing serum thyroid hormone concentrations, PTU produces a high incidence of side effects, which include anorexia, vomiting, lethargy, immune-mediated hemolytic anemia, thrombocytopenia, and the development of serum antinuclear antibodies.[32] Because of the prevalence of severe hematologic complications, the routine use of PTU for control of feline hyperthyroidism is no longer recommended.

METHIMAZOLE. Methimazole is better tolerated and safer than PTU in the cat. It is the antithyroid drug of choice for both the preoperative and long-term medical management of feline hyperthyroidism. Clinical side effects are relatively common (approximately 15%) but mild and include anorexia, vomiting, and lethargy.[33] In most cats they are transient and resolve despite continued drug administration. Severe side effects necessitating discontinuation of therapy are uncommon but include intractable vomiting, diarrhea, anorexia, facial pruritus, hepatotoxicity, and hematologic abnormalities. The latter include thrombocytopenia, agranulocytosis, and hemolytic anemia. Alternative therapy with either surgery or radioiodine should be considered when severe side effects occur.

Initially, methimazole should be administered at a dose of 5 to 15 mg per day given in divided doses bid to tid, depending on the severity of the hyperthyroid state. However, euthyroidism can often be maintained with one daily dose.[4] During the first 3 months of therapy (the period in which the most serious side effects associated with methimazole therapy develop), the cat should be examined every 2 to 3 weeks to make necessary dose adjustments and monitor for adverse effects. At each recheck, serum T_4 concentration and hemogram including platelet count should be determined.[4, 33]

If little or no decrease in the serum T_4 concentration occurs during this initial treatment period, and failure to administer the medication properly has been excluded as the cause of persistent hyperthyroidism, the

daily methimazole dosage should be gradually increased by 2.5- to 5-mg increments. A few cats appear to be relatively resistant to the drug, requiring doses of up to 25 to 30 mg on a daily basis. In cats receiving long-term methimazole treatment, the goal is to maintain serum T_4 values within the low-normal range using the lowest possible daily dosage, since some side effects develop less frequently at lower doses. If serum T_4 concentrations fall excessively, the daily dosage should be decreased by 2.5- to 5-mg increments. Further blood testing should be continued at 2- to 3-week intervals until the lowest daily dose that will effectively maintain serum T_4 concentrations within the low-normal range is attained.[4, 33]

CARBIMAZOLE. Methimazole is currently unavailable in Western Europe and other countries, and the only alternative to PTU is carbimazole. Carbimazole, a carbethoxy derivative of methimazole, is rapidly converted *in vivo* to methimazole. Average starting doses of carbimazole are similar to those of methimazole. However, strict adherence to an 8-hour dosing interval appears to be necessary with carbimazole. Adverse reactions are similar to those of methimazole, although the incidence appears to be less.[4, 34]

CALCIUM OR SODIUM IPODATE. Based upon preliminary data, this agent lowers serum T_3 concentrations, blood pressure, and heart rate in hyperthyroid cats. The dose of 50 mg bid orally appears to be clinically effective for short-term management of mild-to-moderate hyperthyroidism.[34a]

BETA-ADRENERGIC BLOCKING DRUGS. These agents have been used as adjunctive treatment in combination with antithyroid drugs, or alone as a preoperative treatment in hyperthyroid cats that can not tolerate antithyroid drugs. Although propranolol (Inderal, Wyeth-Ayerst) and atenolol (Tenormin, ICI Pharma) do not lower serum thyroid hormone concentrations, both agents block some of the cardiovascular and neuromuscular effects of excess thyroid hormone and may temporarily control related tachycardia, hypertension, or hyperexcitability.[35]

Beta-adrenergic blocking drugs are not advocated for routine therapy of hyperthyroidism. They are reserved for cats with serious tachyarrhythmias, severe systemic hypertension, or when antithyroid drugs (methimazole, carbimazole) cannot be tolerated. They should be used with caution if congestive heart failure is present due their negative inotropic effects. Propranolol is administered at a dosage of 2.5 to 5.0 mg bid to tid, or as required to decrease resting heart rate to normal, reduce hyperexcitability, or control systemic hypertension. Atenolol, a β_1(cardioselective)-adrenergic blocker, may have an advantage over propranolol because of its dosage regimen (6.25 mg once daily), which appears to be effective in most cats.[35, 36]

SURGICAL THYROIDECTOMY

Surgical thyroidectomy can be highly effective in treatment of feline hyperthyroidism, although it can be associated with significant morbidity and mortality (Fig. 34–6).[4, 37–41]

PREOPERATIVE CONSIDERATIONS. Prior to surgery, the cat should be made euthyroid by administration of methimazole antithyroid drug therapy and maintained on this medication for 1 or 2 weeks. Most systemic complications associated with hyperthyroidism will have improved or resolved in this period. This reduces anesthetic risks associated with thyrotoxic arrhythmias or heart failure.[4, 38]

SURGICAL TECHNIQUES. Many techniques for unilateral and bilateral thyroidectomy have been reported.[37–39, 41] Both intracapsular and extracapsular methods have been designed to excise thyroid tissue while preserving parathyroid function. The goal of all techniques is to remove all abnormal thyroid tissue and preserve the function of at least one parathyroid gland.

INTRACAPSULAR TECHNIQUE. The thyroid parenchyma is dissected from the capsule. The external parathyroid gland and its vasculature are preserved, along with the thyroid capsule, thus reducing the chance of hypoparathyroidism. However, if small remnants of thyroid tissue remain attached to the capsule, recurrent hyperthyroidism can occur.

EXTRACAPSULAR TECHNIQUE. The thyroid gland is removed along with its capsule, leaving only the parathyroid glands. The incidence of postoperative hypoparathyroidism can be high with this technique, since parathyroid tissue may be removed or its blood supply destroyed.

MODIFIED EXTRACAPSULAR TECHNIQUE. The thyroid capsule immediately adjacent to the external parathyroid gland is incised and left attached to the parathyroid to preserve its blood supply. This technique results in a relatively low incidence of severe hypoparathyroidism, as well as a low incidence of recurrent hyperthyroidism.[37–39, 41]

POSTOPERATIVE COMPLICATIONS

Many complications accompany thyroidectomy, including hypoparathyroidism, hypothyroidism, Horner's syndrome, renal failure, and laryngeal paralysis (most commonly presenting as dysphonia).

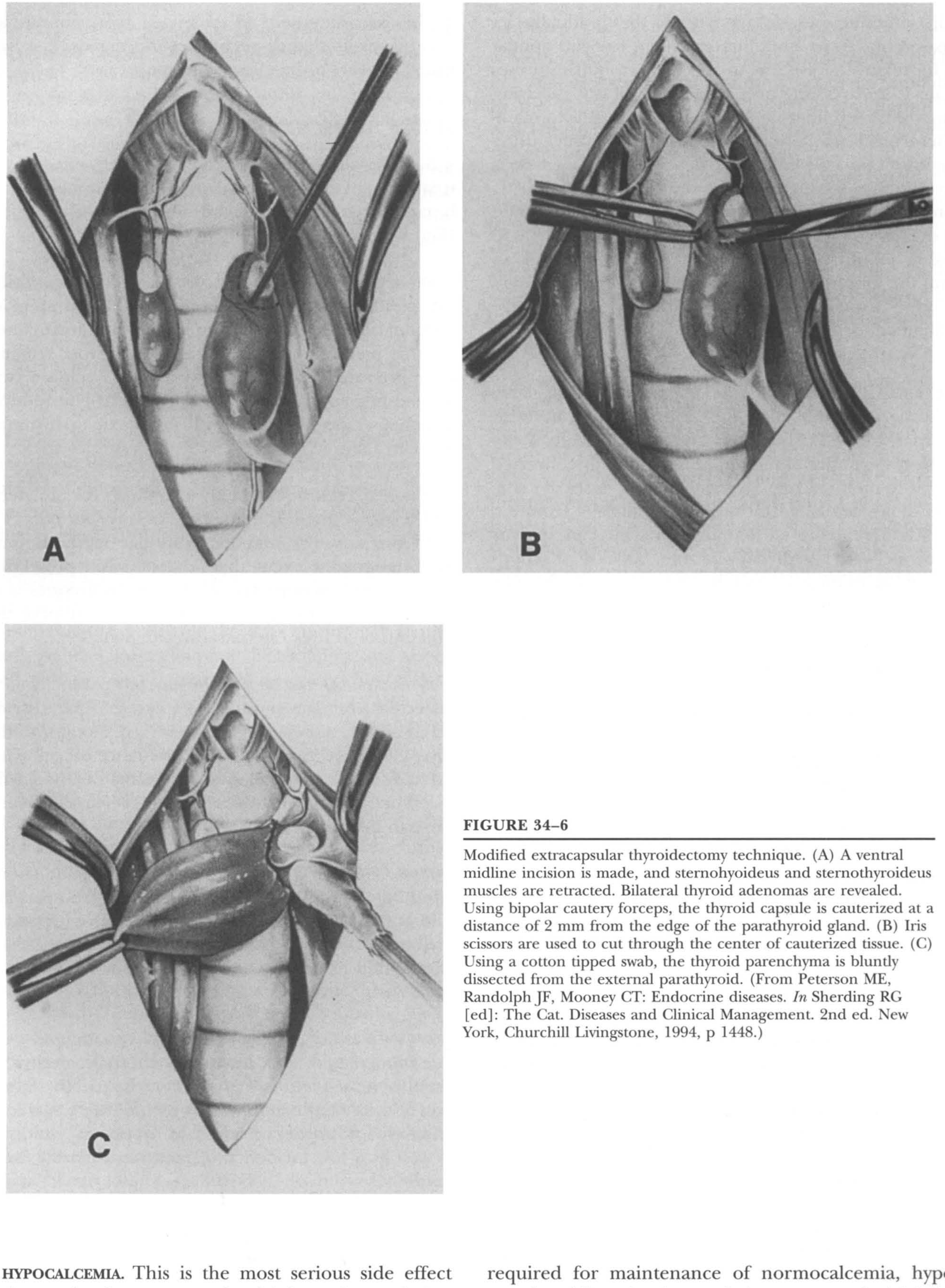


FIGURE 34–6

Modified extracapsular thyroidectomy technique. (A) A ventral midline incision is made, and sternohyoideus and sternothyroideus muscles are retracted. Bilateral thyroid adenomas are revealed. Using bipolar cautery forceps, the thyroid capsule is cauterized at a distance of 2 mm from the edge of the parathyroid gland. (B) Iris scissors are used to cut through the center of cauterized tissue. (C) Using a cotton tipped swab, the thyroid parenchyma is bluntly dissected from the external parathyroid. (From Peterson ME, Randolph JF, Mooney CT: Endocrine diseases. *In* Sherding RG [ed]: The Cat. Diseases and Clinical Management. 2nd ed. New York, Churchill Livingstone, 1994, p 1448.)

HYPOCALCEMIA. This is the most serious side effect and may develop as a result of injury, devascularization, or inadvertent surgical removal of the parathyroid glands.[37, 39–41] Since only one parathyroid gland is required for maintenance of normocalcemia, hypoparathyroidism develops only in cats treated with bilateral thyroidectomy. Clinical signs due to severe hypocalcemia develop within 1 to 3 days after surgery.

Therefore, close postoperative observation is essential after bilateral thyroidectomy, and serum calcium levels should ideally be monitored daily for several days following surgery. Mild hypocalcemia (6.5 to 7.5 mg/dl) is common during the immediate postoperative period. However, therapy is generally not administered unless hypocalcemia is accompanied by muscle fasciculations, tremors, tetany, or convulsions. Electrocardiographic changes are classic and include Q-T interval prolongation (see Fig. 34–3).

Emergency treatment of hypocalcemia consists of intravenous administration of 10 percent calcium gluconate (0.5 to 1.5 mg/kg delivered over 10 to 20 minutes), followed by maintenance calcium and vitamin D supplementation. Hypoparathyroidism may be permanent in some cats, but spontaneous recovery of parathyroid function may occur weeks to months after surgery, at which time therapy can be discontinued.[40]

HYPOTHYROIDISM. Mild hypothyroidism occurs for 2 to 3 months following unilateral thyroidectomy, but serum thyroid hormone concentrations seldom fall low enough to require supplementation. With bilateral thyroidectomy, hypothyroidism tends to be more severe and may be temporary or permanent. If clinical signs of hypothyroidism develop (lethargy, anorexia, obesity, or alopecia), thyroxine should be supplemented (0.1 to 0.2 mg/day). Discontinuation of thyroxine therapy can be attempted after a few months of therapy and monitored serum T_4 administration.

RENAL FAILURE. Treatment of hyperthyroidism can result in impaired renal function. The mean glomerular filtration rate in 13 cats treated for hyperthyroidism decreased from 2.51 to 1.40 ml/kg/min, and two cats developed overt renal azotemia.[42] Thus, blood urea nitrogen (BUN) and creatinine should be monitored after euthyroidism has been re-established.

RECURRENCE OF HYPERTHYROIDISM. This has been reported in 5 to 11 percent of cats after unilateral or bilateral thyroidectomy, occurring 8 to 63 months following surgery.[38, 41, 43] Causes include (1) adenomatous changes in the previously normal gland, (2) ectopic thyroid tumor tissue, or (3) incomplete surgical tumor resection, resulting in remaining thyroid neoplastic tissue.[43] Because of the potential for recurrence, cats treated with surgical thyroidectomy should have serum T_4 concentrations monitored once or twice a year.

RADIOACTIVE IODINE THERAPY

Radioactive iodine (^{131}I) is a simple, effective, safe method for treating feline hyperthyroidism. It is concentrated in the thyroid gland and selectively destroys hyperplastic or neoplastic thyroid tissue. A single ^{131}I treatment will restore euthyroidism in most hyperthyroid cats. Complications of therapy are uncommon and may be easily managed. Cats that remain persistently hyperthyroid can successfully be retreated with radioiodine. Those that become hypothyroid can be readily supplemented with oral thyroxine (T_4). The major disadvantages of ^{131}I therapy are the unavailability of facilities that can safely handle ^{131}I and the prolonged hospitalization that is required due to radiation safety regulations.[4, 44, 45]

ANEMIA

Cardiovascular response to anemia depends upon the rate of red blood cell mass decrease and its magnitude of physiologic corrective mechanisms, and the level of physical and metabolic activities (i.e., oxygen requirements).[46] Unless a coexisting cardiac or hyperkinetic condition is present, anemia usually does not cause heart failure in dogs or cats.

Under some circumstances, however, anemia can impose abnormal hemodynamic alterations and heart failure or precipitate decompensation of compensated heart disease. Severe generalized cardiomegaly was documented in a kitten with severe flea bite anemia (packed cell volume [PCV], 3%). Left-sided congestive heart failure followed whole blood transfusions but was controlled with furosemide. Cardiomegaly resolved by 3 weeks post-therapy.[47] Cardiovascular consequences of severe anemia have been recorded in rats (cardiomegaly and cardiac hypertrophy)[48] and humans (cardiac chamber dilation).[49]

Cardiac output is increased with anemia in dogs and humans.[46, 50, 51] Experimental canine studies revealed that if anemia develops slowly, increased cardiac output results from tachycardia with little change in stroke volume. In chronic, severe anemia, heart rate may be normal or only minimally elevated; cardiac output is increased as a consequence of augmented stroke volume (resulting from a reduction in blood viscosity and systemic arteriolar tone and increased preload). Afterload is decreased because of reduced blood viscosity and reduction in peripheral vascular resistance (from tissue hypoxia and vasodilator metabolites).[46, 50, 52] Vasodilation increases venous blood return (preload). Increased preload and reduced afterload (caused by conditions such as anemia) increase stroke volume and result in a high cardiac output state. Cardiac dilation, hypertrophy, and failure may occur.[50, 51, 53] Hypertrophy associated with volume overload (i.e., eccentric hypertrophy) is characterized by addition of sarcomeres in series resulting in a dilated heart chamber with normal wall thickness.[54] In humans, a sustained increase in cardiac output occurs when the hematocrit falls below 25 percent (unless anemia is

associated with a disease that produces an increase in viscosity such as multiple myeloma).[1]

Clinical manifestations of anemia include weakness, pale mucous membrane color, hyperkinetic femoral arterial pulses, soft systolic cardiac murmur, gallop rhythm, eccentric cardiac hypertrophy, generalized cardiomegaly, and high-output heart failure.[1, 55] These changes are largely reversible with therapy.

If congestive heart failure occurs in an anemic animal, cage rest and furosemide are used to control extracardiac signs of effusion or pulmonary edema. Slow transfusion (over 4 hours) of packed red blood cells (RBC) is recommended (6 to 10 ml of undiluted RBCs/kg reconstituted in a minimal quantity of saline to facilitate the infusion).[56] The pet should be reassessed every 6 hours for the next 24 hours to decide whether repeat transfusion is necessary. The underlying cause of anemia must be identified and corrected if possible. Inotropic support (dobutamine, 2 to 5 μg/kg at a constant rate infusion) may be added if systolic (myocardial) failure is present. Vasodilators are probably of little help, as impedance to left ventricular emptying is already reduced.[1]

Transfusion-associated circulatory overload resulting in pulmonary congestion has been reported in humans.[57] This may occur even in a setting of modest transfusion volumes in humans and has occasionally been observed in cats.

ARTERIOVENOUS FISTULAS

Arteriovenous (AV) fistulas (arteriovenous malformations) are congenital or acquired abnormal communications between arteries and veins that bypass the capillary network. Acquired causes are usually iatrogenic or traumatic, resulting from blunt or penetrating trauma, but AV fistulas may also result from infiltrative neoplasm or infection.[58–61] Communications of the cardiac chambers (e.g., ventricular septal defects) or great vessels (e.g., patent ductus arteriosus) may occur as a centrally located anomaly (chapter 24).[62]

PATHOPHYSIOLOGY

Arteriovenous fistulas act to bypass normal blood flow (chapter 33). Initially, this reduces peripheral vascular resistance and decreases circulation to tissues served by the affected artery. With most peripheral shunts, flow to tissue distal to the shunt is maintained through collateral circulation, which develops by dilation of pre-existing unused arterioles. Therefore, venous hypertension and increased venous return to the heart occur. Hemodynamic responses to restore arterial blood volume and perfusion include increased heart rate and peripheral vasoconstriction. Left ventricular stroke volume increases, and cardiac output may elevate as much as two to three times above normal. The magnitude of these changes depends primarily on the size of the fistula and affected artery, and proximal arterial blood flow velocity.[58, 60]

Chronic effects of AV fistulas are due to elevated cardiac output resulting from increased venous return and decreased peripheral vascular resistance. These changes in blood volume and cardiac output expand the fistulous circuit, increasing blood flow and cardiac preload. Congestive circulatory failure may ensue. Eventually, elevated venous pressure, pulmonary congestion, and edema can result. Mitral valvular insufficiency and myocardial failure secondary to volume overload may develop and contribute to congestive heart failure.[1, 53]

DIAGNOSIS

PHYSICAL EXAMINATION

Clinical history and signs vary according to location, size, duration, and etiology. With large peripheral AV fistulas, involved arteries may be dilated; venous pulsation may be evident; and a continuous focal vascular murmur (bruit) and palpable thrill over the AV fistula area can be detected. Manual occlusion of the fistula often causes Branham's sign, an abrupt slowing of the heart rate. Hyperthermia may be noted over the fistula, and the distal limb may be edematous, swollen, ischemic, and painful. There is a widened arterial pulse pressure due to a decrease in peripheral vascular resistance and rapid diastolic runoff into the venous circulation. Small AV fistulas of the extremities are noticed as painless, easily compressible, warm bulges.[1, 53, 60]

DIAGNOSTIC IMAGING

Angiography can be useful preoperatively to evaluate fistula anatomy and location and help guide surgery. Diagnostic ultrasound, especially color flow Doppler echocardiography, may be clinically useful to identify and localize fistulas.[59] Findings include identification of intra-arterial flow at the fistula site throughout the cardiac cycle; turbulent, pulsatile venous flow at the fistula site; and nonpulsatile venous flow proximal to the fistula. This may result in continuous flow imaged by spectral Doppler echocardiography (Fig. 34–7). The communication between artery and vein may sometimes be identified.

THERAPY

Surgical ligation or excision of the AV fistula has been the treatment of choice, unless myocardial failure

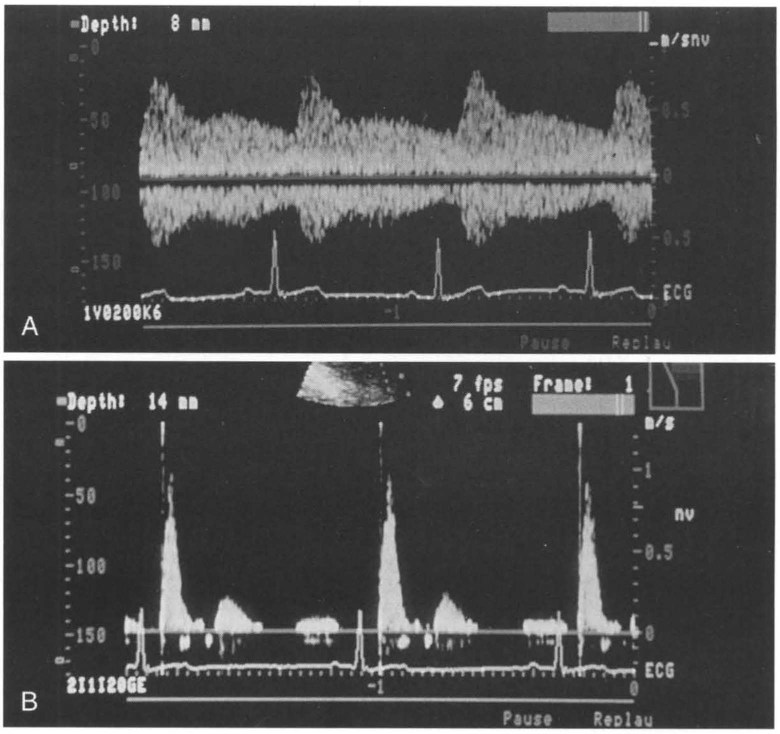


FIGURE 34–7

Recordings from a dog with traumatic AV fistula. (A) Pulsed-wave Doppler recording of a large, pulsatile, dilated vessel associated with the right radial artery. Notice the continuous flow, especially in diastole. (B) Pulsed-Doppler flows recorded from the normal left radial artery in the same dog. (From Suter PF, Fox PR: Peripheral vascular disease. *In* Ettinger SJ, Feldman EC: Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1992, p 1074.)

or pulmonary hypertension is present. Caution must be observed before surgically correcting fistulas. Their repair may abruptly increase peripheral vascular resistance and increase myocardial stress. Diuretic administration may be necessary prior to surgical ligation.[60] Nonsurgical transcatheter coil occlusion has been accomplished in a cat with a peripheral AV fistula, suggesting an alternate technique to surgery in selected cases (Fox PR, unpublished data, 1997).

REFERENCES

1. Braunwald E, Grossman W. Clinical aspects of heart failure. *In* Braunwald E (ed): Heart disease. 4th ed. Philadelphia, WB Saunders, 1992, p 458
2. Gordon HW, Braunwald E. Endocrine and nutritional disorders in heart disease. *In* Braunwald E (ed): Heart disease. 4th ed. Philadelphia, WB Saunders, 1992, p 1827
3. Klein I, Levey GS. New perspectives on thyroid hormone, catecholamines, and the heart. Am J Med 76:167, 1984
4. Peterson ME. Hyperthyroid diseases. *In* Ettinger SJ, Feldman ED (eds): Textbook of Veterinary Internal Medicine. 4th ed, Philadelphia, WB Saunders, 1995, p 1446
5. Turrel JM, Feldman EC, Nelson RW, et al. Thyroid carcinoma causing hyperthyroidism in cats: 14 cases (1981–1986). J Am Vet Med Assoc 193:359, 1988
6. Guptill L, Scott-Moncrieff JCR, Janovitz EB, et al. Response to high-dose radioactive iodine administration in cats with thyroid carcinoma that had previously undergone surgery. J Am Vet Med Assoc 207:1055, 1995
7. Peterson ME, Kintzer PP, Cavanagh PG, et al. Feline hyperthyroidism: pretreatment clinical and laboratory evaluation of 131 cases. J Am Vet Med Assoc 183:103, 1983
8. Cohen MV, Schulman IC, Spenillo A, et al. Effects of thyroid hormone on left ventricular function in patients treated for thyrotoxicosis. Am J Cardiol 48:33, 1981
9. Forfar JC, Muir AL, Sawyers MB, et al. Abnormal left ventricular function in hyperthyroidism: evidence for a possible reversible cardiomyopathy. N Engl J Med 307:1165, 1982
10. Dillman WH. Thyroid hormones and the heart. Thyroid Today 6:1, 1983
11. Lewis BS, Ehrenfeld EN, Lewis N, et al. Echocardiographic left ventricular function in thyrotoxicosis. Am Heart J 97:460, 1979
12. Nixon JV, Anderson RJ, Mitchell LC. Alterations in left ventricular performance in patients treated effectively for thyrotoxicosis. Am J Med 67:268, 1979
13. Parmacek MS, Magid NM, Lesch M, et al. Cardiac protein synthesis during thyroxine-induced left ventricular hypertrophy. Am J Physiol 251 (Cell Physiol 20):C727, 1986
14. Shafer RB, Bianco JA. Assessment of cardiac reserve in patients with hyperthyroidism. Chest 78:269, 1980
15. Bond BR, Fox PR, Peterson ME, et al. Echocardiographic findings in 103 cats with hyperthyroidism. J Am Vet Med Assoc 192:1546, 1988
16. Moise NS, Dietze AE. Echocardiographic, electrocardiographic, and radiographic detection of cardiomegaly in hyperthyroid cats. Am J Vet Res 47:1487, 1986
17. Moise NS, Dietze AE, Mezza LE, et al. Echocardiography, electrocardiography, and radiography of cats with dilatation cardiomyopathy, hypertrophic cardiomyopathy, and hyperthyroidism. Am J Vet Res 47:1476, 1986
18. Broussard JD, Peterson ME, Fox PR. Changes in clinical and laboratory findings in cats with hyperthyroidism from 1983 to 1993. J Am Vet Med Assoc 206:302, 1995
19. Graves TK, Peterson ME. Diagnosis of occult hyperthyroidism in cats. Probl Vet Med 2:683, 1990

20. Fox PR, Broussard JD, Peterson ME. Electrocardiographic and radiographic changes in cats with hyperthyroidism: 1979–1982 vs. 1992. Abstract. J Vet Intern Med 7:118, 1993
21. Jacobs G, Hutson C, Dougherty J, et al. Congestive heart failure associated with hyperthyroidism in cats. J Am Vet Med Assoc 188:52, 1986
22. Jacobs G, Panciera D. Cardiovascular complications of feline hyperthyroidism. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1992, p 756
23. Liu SK, Peterson ME, Fox PR. Hypertrophic cardiomyopathy and hyperthyroidism in the cat. J Am Vet Med Assoc 185:52, 1984
24. Atkins CE. Thyrotoxic heart disease. *In* August J (ed): Consultations in Feline Internal Medicine. 3rd ed. Philadelphia, WB Saunders, 1996, p 279
25. Thoday KL, Mooney CT. Historical, clinical and laboratory features of 126 hyperthyroid cats. Vet Rec 131:257, 1992
26. Peterson ME, Keene B, Ferguson DC, et al. Electrocardiographic findings in 45 cats with hyperthyroidism. J Am Vet Med Assoc 180:934, 1982
26a. Peterson ME, Melian Liminana C, Nichols CE. Determination of free T_4 by dialysis as an aid in diagnosis of mild hyperthyroidism in cats. J Vet Intern Med 9:183, 1995
27. McLoughlin MA, DiBartola SP, Birchard SJ, et al. Influence of systemic nonthyroidal illness on serum concentration of thyroxine in hyperthyroid cats. J Am Anim Hosp Assoc 29:227, 1993
28. Peterson ME, Graves TK, Cavanagh PG, et al. Serum thyroid hormone concentrations fluctuate in cats with hyperthyroidism. J Vet Intern Med 1:142, 1986
29. Refsal KR, Nachreiner RF, Stein BE, et al. Use of the triiodothyronine suppression test for diagnosis of hyperthyroidism in ill cats that have serum concentration of iodothyronines within normal range. J Am Vet Med Assoc 199:1594, 1991
30. Peterson ME, Becker DV. Radionuclide imaging in 135 cats with hyperthyroidism. Vet Radiol 25:23, 1984
31. Franklyn JA. The management of hyperthyroidism. N Engl J Med 330:1731, 1994
32. Peterson ME, Hurvitz AI, Leib MS, et al. Propylthiouracil-associated anemia, thrombocytopenia, and antinuclear antibodies in cats with hyperthyroidism. J Am Vet Med Assoc 184:806, 1984
33. Peterson ME, Kintzer PP, Hurvitz AI. Methimazole treatment of 262 cats with hyperthyroidism. J Vet Intern Med 2:150, 1988
34. Mooney CT, Thoday KL, Doey DL. Carbimazole therapy of feline hyperthyroidism. J Small Animal Pract 33:228, 1992
34a. Murray LAS, Peterson ME. Ipodate treatment of hyperthyroidism in cats. J Vet Med Assoc 211:63, 1997
35. Peterson ME. Consideration and complications in anesthesia with pathophysiologic changes in the endocrine system. *In* Short CE (ed): Principles and Practice of Veterinary Anesthesiology. Baltimore, Williams and Wilkins, 1987, p 251
36. Thoday KL, Mooney CT. Medical management of feline hyperthyroidism. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1992, p 338
37. Birchard SJ. Thyroidectomy and parathyroidectomy in the dog and cat. Probl Vet Med 3:277, 1991
38. Salisbury SK. Hyperthyroidism in cats. Compend Contin Educ Pract Vet 13:1399, 1991
39. Welches CD, Scavelli TD, Matthiesen DT, et al. Occurrence of problems after three techniques of bilateral thyroidectomy in cats. Vet Surg 18:392, 1989
40. Peterson ME. Hypoparathyroidism and other causes of hypocalcemia in cats. *In* Kirk RW, Bonagura JD (eds): Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1992, p 376
41. Flanders JA, Harvey HJ, Erb HN, et al. Feline thyroidectomy. A comparison of postoperative hypocalcemia associated with three different surgical techniques of bilateral thyroidecomy in cats. Vet Surg 16:362, 1987
42. Graves TK, Olivier B, Nachreiner RF, et al. Changes in renal function associated with treatment of hyperthyroidism in cats. Am J Vet Res 55:1745, 1994
43. Swalec KM, Birchard SJ. Recurrence of hyperthyroidism after thyroidectomy in cats. J Am Anim Hosp Assoc 26:433, 1990
44. Peterson ME. Radioactive iodine (radioiodine) treatment for hyperthyroidism in cats. *In* Bonagura JD (ed): Kirk's Current Veterinary Therapy. Vol XII. Philadelphia, WB Saunders, 1995, p 372
45. Turnel JM, Feldman EC, Hays M, et al. Radioactive iodine therapy in cats with hyperthyroidism. J Am Vet Med Assoc 184:554, 1984
46. Linman JW. Physiologic and pathophysiologic effects of anemia. N Engl J Med 279:812, 1968
47. Yaphé W, Giovengo S, Moise NS. Severe cardiomegaly secondary to anemia in a kitten. J Am Vet Med Assoc 202:961, 1993
48. Rossi MA, Carillo SV, Oliveira JSM. The effect of iron deficiency anemia in the rat on catecholamine levels and heart morphology. Cardiovasc Res 15:313, 1981
49. Balfour IC, Covitz W, Davis H, et al. Cardiac size and function in children with sickle cell anemia. Am Heart J 108:345, 1984.
50. Vatner SF, Higgins CB, Franklin D. Regional circulatory adjustments to moderate and severe chronic anemia in conscious dogs at rest and during exercise. Circ Res 30:731, 1972
51. Ingram CW, Satler LF, Rackley CE. Progressive heart failure secondary to a high output state. Chest 92:1117, 1987
52. Fowler NO, Holmes JC. Blood viscosity and cardiac output in acute experimental anemia. J Appl Physiol 39:453, 1975
53. Rosenthal DS, Braunwald E. Hematological-oncological disorders and heart disease. *In* Braunwald E (ed): Heart Disease. A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB Saunders, 1992, p 1742
54. Katz AM. Cardiomyopathy of overload. N Engl J Med 322:100, 1990
55. Varat MA, Adolph RJ, Fowler NO. Cardiovascular effects of anemia. Am Heart J 83:415, 1972
56. Hohenhaus A. Unpublished data, 1995
57. Popovsky MA, Dedham, MA, Audet AM, et al. Transfusion-associated circulatory overload in orthopedic surgery patients: a multi-institutional study. Abstract. Transfusion 35 (Suppl):35S, 1995
58. Olivier NB. Pathophysiology of arteriovenous fistulae. *In* Slatter DH (ed): Textbook of Small Animal Surgery. Philadelphia, WB Saunders, 1985, p 923
59. Igidbashian VN, Mitchell DG, Middleton WD, et al. Iatrogenic femoral arteriovenous fistula: diagnosis with color flow Doppler imaging. Radiology 170:749, 1989
60. Suter PF, Fox PR. Diseases of the peripheral vessels. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine. Vol 2. 4th ed. Philadelphia, WB Saunders, 1995, p 1068

61. Bouayard H, Feeney DA, Lipowitz AJ, et al. Peripheral acquired arteriovenous fistulas: a report of four cases and literature review. J Am Anim Hosp Assoc 23:205, 1987

62. Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine Vol 2. 4th ed. Philadelphia, WB Saunders, 1995, p 892

35

Systemic Hypertension: Recognition and Treatment

MERYL P. LITTMAN
PHILIP R. FOX

THE EMERGING REALITIES OF HYPERTENSION AND DISEASE

DEFINITION OF HYPERTENSION

The question, "What level of elevated blood pressure (i.e., hypertension) should be treated?" is the subject of much debate in humans and has not been answered for dogs and cats. Conceptually, the level of hypertension requiring treatment should be that at which the benefits of therapy (minus risks and costs) exceed risks and costs (minus benefits) of inaction.[1] The answer to the corollary question, "To what level should blood pressure be reduced?" is also unclear[2] and has received little veterinary attention.

The diagnosis of hypertension should be substantiated by repeated evaluations, since fright or excitement may cause elevated recordings. The very act of taking blood pressure measurement in humans elevates blood pressure. In one study, a 27-mmHg rise in systolic pressure was attributable to physician presence.[3] This "white coat syndrome" may also exist with animals.

Reports of normal blood pressures in animals vary according to investigator and technique (Table 35–1).[4–22] Ideally, normal values should be established by the clinician utilizing equipment and techniques available.

Blood pressure varies with age, body condition, gender, and breed in dogs.[23] The frequency of hypertension increases with age in humans.[24, 25] In dogs, both systolic and diastolic blood pressure rise with increasing age, up to late middle age (Table 35–2). The young dog with a rapid heart rate tends to have lower blood pressure than the adult. Body condition also affects canine blood pressure, with lower blood pressure recorded in healthy underweight dogs compared with overweight dogs. In humans and dogs, obesity is a predictor and concomitant of hypertension,[4, 26] and resolution of obesity reduces blood pressure.[4, 27] Male dogs may be predisposed to hypertension.[15, 23, 28–31] Additionally, blood pressure may vary widely according to canine breed (Table 35–3).[23]

TABLE 35–1
Arterial Blood Pressure Measurements from Untrained, Conscious Dogs and Cats

Method	Systolic BP	Diastolic BP	Mean Arterial BP
	Canine		
Direct			
Aortic[4]	128 ± 5	74 ± 6	90 ± 5
Carotid[5]	141 ± 22.8	99 ± 14.7	113 ± 16.1
Femoral[6]	148 ± 16	87 ± 8	102 ± 9
Femoral[5]	154 ± 30.5	96 ± 11.9	115 ± 16.2
Femoral[7]	200–240*	80–100*	120–147*
Femoral[8]	144 ± 2.8	81 ± 1.7	104 ± 2.5
Femoral[9]†	200 ± 22.4	91.6 ± 18.6	
Femoral[10]			90–150
Indirect			
Auscultatory[11]	94–178	51–111	
Auscultatory[12]	132 ± 17.2	93.4 ± 15.7	106.3 ± 15.6
Auscultatory[10]	100–180	60–120	
Oscillometric[13]	87.8–155.6	63.0–122.8	70.8–136
Oscillometric[5]	152 ± 38.4	104 ± 22.8	120 ± 25.2
Oscillometric[14]	144 ± 27	91 ± 20	110 ± 21
Doppler[15]	164 ± 24	91 ± 18	
Doppler[5]	145 ± 22.5		
Doppler[16]	147 ± 28	83 ± 15	104 ± 17
Doppler[17]	155 ± 25	85 ± 10	
Doppler[9]†	196 ± 24.9	94.1 ± 14	
Xylol pulse indicator[18]	142 ± 14.9		
	Feline		
Direct			
Femoral[19]	171.3 ± 22.4*	123.0 ± 17.4*	
Femoral[20]	113	83	
Indirect			
Oscillometric[13]	117–149	48–102	61–124
Doppler[21]	118.4 ± 10.6	83.8 ± 12.2	
Doppler[20]	113	85	
Doppler[22]	143 ± 7	96 ± 9	

*Animals described as anxious or uncooperative.
†Greyhounds.

TABLE 35–2
Changes in Blood Pressure Associated with Changing Age (Healthy Dogs Only)

Age Range (years)	Number of Dogs	Systolic BP Mean ± SD (mmHg)	Diastolic BP Mean ± SD (mmHg)	Mean Arterial Pressure Mean ± SD (mmHg)	Heart Rate Mean ± SD (bpm)
0–1	271	119.0 ± 17.7	65.7 ± 12.6	86.9 ± 13.8	124.3 ± 28.8
1–2	296	128.2 ± 18.7	70.9 ± 12.8	93.9 ± 14.5	105.7 ± 25.6
2–4	392	131.9 ± 20.1	74.3 ± 15.0	97.2 ± 16.8	104.4 ± 24.6
4–6	220	138.4 ± 22.8	78.1 ± 17.3	101.8 ± 18.8	108.4 ± 28.9
6–8	148	136.1 ± 19.6	77.2 ± 15.7	100.9 ± 16.1	109.2 ± 26.0
8–10	116	139.2 ± 17.4	80.5 ± 14.4	104.2 ± 15.6	109.0 ± 23.5
10–12	59	140.6 ± 20.5	85.6 ± 15.6	108.0 ± 16.9	105.1 ± 18.4

From Bodey AR. Systemic hypertension in the dog—fact or fiction? Proceedings, 18th Annual Waltham/OSU Symposium: Cardiology. Vernon, CA, 1994, p 44, with permission.

TABLE 35-3
Breed Differences in Blood Pressure (Healthy Dogs Only, 18 Months Old Plus)

Breed	Number of Dogs	Systolic BP Mean ± SD (mmHg)	Diastolic BP Mean ± SD (mmHg)	Mean Arterial Pressure Mean ± SD (mmHg)	Heart Rate Mean ± SD (bpm)
Labrador	125	118.6 ± 17.1	66.2 ± 13.1	87.1 ± 14.7	99.2 ± 19.7
Pyrenean mountain dog	32	120.1 ± 16.0	66.7 ± 6.5	90.2 ± 9.9	95.4 ± 15.6
Golden retriever	66	122.4 ± 13.9	69.5 ± 11.2	92.4 ± 12.1	101.2 ± 21.4
Border collie	34	130.6 ± 13.5	75.0 ± 12.0	97.8 ± 12.9	100.0 ± 19.3
Cavalier King Charles spaniel	60	131.3 ± 16.1	72.3 ± 14.0	96.4 ± 14.5	124.5 ± 24.6
German shepherd dog	42	131.6 ± 13.1	74.7 ± 10.4	98.2 ± 13.1	108.5 ± 23.0
Saluki	37	142.7 ± 16.2	78.4 ± 9.9	102.2 ± 10.7	88.4 ± 22.1
Greyhound	78	149.2 ± 20.2	87.5 ± 16.1	111.0 ± 17.3	114.2 ± 28.1
Deerhound	96	152.0 ± 20.2	86.9 ± 17.0	112.0 ± 17.2	95.8 ± 23.1

From Bodey AR. Systemic hypertension in the dog—fact or fiction? Proceedings, 18th Annual Waltham/OSU Symposium: Cardiology. Vernon, CA, 1994, p 44, with permission.

CLINICAL SIGNIFICANCE OF HYPERTENSION

Systemic hypertension is a major human risk factor for coronary, cerebral, and renal vascular diseases.[25] Data show that even mild hypertension increases the overall risk for premature cardiovascular morbidity and mortality. Coupled with evidence that cardiovascular disease progression can be reduced by drug administration, these realities have heightened awareness of the dangers associated with untreated hypertension and have led to aggressive therapy.

Increasingly, systemic hypertension has been recognized as a cause or consequence of clinical disease in cats[21, 32–37] and dogs.[8, 17, 23, 28, 29, 38–51] In contrast to humans, in whom most hypertension is primary[52] (i.e., essential), canine and feline hypertension is usually associated with systemic diseases.

INCIDENCE OF HYPERTENSION

Lack of simple, convenient, and dependable techniques for noninvasive blood pressure measurement has limited detection and assessment of the natural prevalence. These restrictions are being overcome as methods for indirect blood pressure monitoring are studied and validated in dogs[16, 17, 53–55] and cats.[20–22, 32, 56–58] Occasionally, markedly elevated blood pressures requiring intervention are documented, with acute blindness, retinal detachment or hemorrhage, or neurologic signs.[28, 29, 32–34, 47, 50] In other cases elevated blood pressure is associated with asymptomatic or mildly systemic diseases, but therapy is deemed appropriate to reduce risk of end-organ injury.[17, 21, 28, 36] With many disorders, blood pressure elevations may be mildly to moderately elevated but not deemed high enough to constitute immediate danger.[6, 21, 35, 36]

In cats, a high percentage of hypertension has been reported with certain systemic diseases. One report of 40 cats with hyperthyroidism, chronic renal insufficiency, or hypertrophic cardiomyopathy showed hypertension in 19 (47.5%) as assessed with Doppler-shift sphygmomanometry; of these 19, 9 had elevated systolic blood pressure only (164 ± 17 mmHg), and 10 had diastolic (118 ± 19 mmHg) and systolic hypertension.[35] In a different series of 28 cats with chronic renal failure, the overall mean systolic (147 ± 25 mmHg) and mean diastolic (97 ± 15 mmHg) blood pressure was significantly greater than controls, and systemic hypertension was recorded in 17 (61%) affected cats.[21] Similarly, in 39 cases of untreated feline hyperthyroidism, 87 percent were hypertensive (mean systolic, 168 ± 29 mmHg; mean diastolic, 112 ± 22 mmHg).[21] A study of 24 cats with end-organ damage showed systemic hypertension by Doppler in 17 cats (mean systolic, 219 ± 43 mmHg) and by femoral arterial puncture in 15 cats (mean systolic 233 ± 41; mean diastolic 148 ± 29 mmHg); mild renal insufficiency was present in all but one animal (which had moderate-to-severe renal insufficiency), and three cats were hyperthyroid.[32]

Canine studies[6, 8, 11, 14, 17, 28, 29, 38–46, 59] have reported both primary and secondary forms of hypertension. In dogs with documented hypertension and end-organ damage, renal disease was detected in about 30 to 40 percent; hyperadrenocorticism (either pituitary-dependent or due to adrenal tumor) was detected in another 30 to 40 percent.[28, 29] Essential hypertension has been documented in some dogs.[28, 29, 47, 50] Rarely, hypertension is detected in dogs secondary to pheochromocytoma[60] or polycythemia.[17] A number of diseases that can cause hypertension in humans also have been reported in the dog, although hypertension has not yet been documented. These conditions include hyperaldosteronism, hypothyroidism, aortic coarctation, hyperestrogenism, acromegaly, brain tumors, and lead or vitamin D toxicity. Although hypertension was reported in dogs with low serum thyroxine (T_4), hypothyroidism was not proved by thyroid-stimulating hormone (TSH).[41, 45]

REGULATORY MECHANISMS OF BLOOD PRESSURE

Regulation of systemic blood pressure is influenced by central and peripheral autonomic and neuroendocrine mechanisms.[61] These control blood volume, heart rate, and vasomotor tone. Additionally, local vascular factors affect the myointimal intracellular ionic milieu. Total peripheral resistance is influenced by vasomotor tone and blood viscosity. Vasoactive chemicals may affect vasodilation or constriction. Factors such as intracellular sodium and calcium may alter arteriolar sensitivity to these chemical agents.

Physical or pathologic conditions like arteriosclerosis or atherosclerosis may affect arteriolar structure by reducing vascular elasticity and luminal diameter. Blood itself may influence peripheral resistance by nature of its viscosity, hematocrit, and red cell deformability.[62–64]

THE SYSTEMIC CIRCULATION

The circulatory system is divided into the systemic and pulmonary circulations (chapter 2). The total cross-sectional vascular area is greatest in the capillaries. Blood pressure and resistance are intimately related and vary according to each particular segment of systemic circulation.

NORMAL BLOOD PRESSURE

Blood pressure fluctuates throughout the day and night, as demonstrated by ambulatory 24-hour blood pressure measurements in dogs.[65] Additionally, blood pressure measurements may increase with handling, feeding, noise, and in the early morning.[55, 66–68] Blood flow is not a fixed entity. It is influenced by (1) the amount of pressure forcing blood through the vessel, and (2) the resistance to flow.[69, 70]

INTERRELATIONSHIPS: BLOOD PRESSURE, BLOOD FLOW, AND RESISTANCE

Blood pressure (BP) can be expressed as the product of cardiac output (CO) multiplied by total peripheral resistance (TPR): BP = CO × TPR. Cardiac output is represented by the product of heart rate (HR) multiplied by stroke volume (SV): CO = HR × SV. Stroke volume is influenced by cardiac contractility, preload, and afterload (chapter 2). Thus, alterations in blood characteristics, extracellular fluid (blood) volume, and cardiac factors will markedly influence blood pressure. Arteriolar resistance is the major determinant of blood pressure at rest; during exercise, CO assumes a more important role. In addition, both HR and TPR are modulated by other factors, including the renal body-fluid system, the renin-angiotensin-aldosterone system, and neural mechanisms (discussed later). Sympathetic nervous system stimulation causes direct vasoconstriction, as well as adrenal medullary release of epinephrine and norepinephrine, which indirectly stimulates cardiac and vascular smooth muscle. In addition, angiotensin II enhances release of norepinephrine from the adrenergic nervous system.

The Poiseuille equation highlights the importance of blood vessel diameter as the key determinant of resistance:

$$Q = \frac{\pi \Delta P r^4}{8 L \eta}$$

where Q = flow, $\pi/8$ = proportionality constant, ΔP = pressure gradient, r = radius, L = vessel length, and η = blood viscosity. This demonstrates that flow is directly proportional to the pressure gradient and to the fourth power of the vessel's diameter, and inversely proportional to the vessel length and blood viscosity. Arterioles are well-muscled vessels that offer the greatest resistance to flow. Resistance begins increasing rapidly in small arteries and is greatest in the arterioles.[61]

MEAN ARTERIAL PRESSURE (MAP). This represents the average pressure throughout the cardiac cycle and is used as an approximation of arteriolar resistance.[71] The MAP is slightly less than the value halfway between systolic (SBP) and diastolic (DBP) pressures and may be approximated by the equation:

$$MAP = \frac{(SBP + 2DBP)}{3}$$

RAPIDLY ACTING MECHANISMS CONTROLLING BLOOD PRESSURE

NERVOUS SYSTEM MECHANISMS

The central nervous system (CNS) controls both peripheral autonomic nervous system activity and release of circulating hormonal factors. Thus, it acutely modifies blood pressure and heart rate to promote cardiovascular homeostasis.[72]

Sympathetic nervous system stimulation causes direct vasoconstriction. Adrenal medullary release of epinephrine and norepinephrine indirectly stimulates cardiac and vascular smooth muscle. In addition,

angiotensin II enhances norepinephrine release from the adrenergic nervous system.

The *baroreceptor reflex* is initiated by stretch receptors in walls of the carotid sinus and aortic arch. The receptors convey sensory signals to the brain stem vasomotor center in response to changes in arterial blood pressure. A fall in pressure decreases baroreceptor impulses to the vasomotor center. This increases sympathetic efferent traffic and causes vasoconstriction, raises heart rate, and increases blood pressure. An increase in blood pressure causes the opposite reaction. Additional pressure receptors in the atria and pulmonary arteries assist arterial pressure regulation.

The *chemoreceptor reflex* is normally less important for blood pressure control. Responding presumably to acidosis or hypercapnia, chemoreceptors located in the carotid and aortic bodies transmit afferent signals to excite the vasomotor center and increase blood pressure.

HORMONAL MECHANISMS

The renin-angiotensin-aldosterone system plays an important role in cardiovascular homeostasis.[73, 74] Angiotensin II is one of the most potent vasoconstrictors. In hypotensive states, or if renal perfusion is low due to various mechanisms, juxtaglomerular cells in the afferent arteriolar walls secrete the enzyme renin into the blood, which hydrolyzes angiotensinogen to the decapeptide angiotensin I. In pulmonary vessels, angiotensin-converting enzyme (ACE) catalyzes formation of the octapeptide angiotensin II from angiotensin I. As a potent arteriolar vasoconstrictor (venoconstrictor effects are milder), angiotensin II enhances adrenergic release of norepinephrine. Along with increased adrenergic activity, it contributes to increased total peripheral resistance, afterload, and arterial blood pressure. Angiotensin II also stimulates the adrenal cortex to secrete the mineralocorticoid aldosterone, which promotes renal Na^+ and fluid retention, and raises blood volume (preload).

LONG-TERM REGULATION OF ARTERIAL BLOOD PRESSURE

Many of the short-term mechanisms affecting blood pressure become diminished over time.[70] Mechanisms for more sustained pressure control rely on interrelationships between the kidney and vascular fluid interaction and are augmented by neurohumoral systems.

RENAL-FLUID VOLUME MECHANISM

The renal-fluid volume mechanism is so powerful that it allows the kidneys to exert the dominant force for long-term pressure control. The kidney uses two major mechanisms. One acts by manipulating extracellular fluid volume, which, in turn, affects blood volume, cardiac output, and arterial pressure. Elevated arterial blood pressure increases renal excretion of sodium and water. Referred to as pressure natriuresis and pressure diuresis, this reduces extracellular fluid volume through increased urine output. Conversely, renal excretion of salt and water is reduced when arterial pressure drops. Several physiologic mechanisms enhance this system of pressure control, including the second mechanism, which involves the renin-angiotensin-aldosterone system and adrenergic system as described earlier.[75]

LOCAL CONTROL OF BLOOD FLOW

A complex and interrelated set of homeoregulatory mechanisms affects the circulatory system to regulate blood flow. The mechanisms include humoral, nervous, and local control.[70]

HUMORAL REGULATION. At the cellular level, vasomotor tone depends on the final common pathway: cytosolic Ca^{++} availability to interact with smooth muscle myosin. Cytosolic Ca^{++} depends on flux of other cations (e.g., Na^+, K^+, Mg^{++}). Many countertransports exist. The pressor effect of Na^+ depends on Ca^{++} since increased intracellular Na^+ is associated with increased cytosolic Ca^{++}.[76, 77] The spontaneously hypertensive rat (SHR) on a high NaCl diet secretes much less endothelium-derived relaxing factor (EDRF, which may be nitric oxide) than normal, but if supplemented with high K^+, will secrete EDRF normally. Platelet adhesion to endothelial cells and platelet aggregation are inhibited by EDRF. In hypertensives without enough EDRF, there is high risk for thrombosis; K^+ is protective.[78]

Many agonists (including angiotensin II, serotonin, and catecholamines via post-synaptic α_1-receptors), when bound to their G-protein cell membrane receptor, act via phospholipase C (PLC) to generate intracellular second messenger modulators.[79] The activation of PLC releases diacylglycerol (DG) and inositol triphosphate (IP_3): DG activates a Ca^{++}-dependent protein kinase (PKC) that controls a Na^+-H^+ membrane exchange system; inositol triphosphate directs cytosolic Ca^{++} from the sarcoplasmic reticulum, freeing it for action with vascular smooth muscle myosin. Angiotensin, norepinephrine, and thromboxane A_2 stimulate contraction, whereas EDRF, kallikrein, bradykinin, and prostacyclin relax vascular smooth muscle.

AUTONOMIC NERVOUS SYSTEM REGULATION. The vasomotor center is capable of stimulating vasoconstriction or inhibiting it, depending upon which area is activated.[61] Sympathetic stimulation to the small arteries

and, especially, arterioles increases total systemic vascular resistance. Venous stimulation increases blood return to the heart. Cardiac stimulation increases heart rate and force of contraction. Parasympathetic stimulation reduces heart rate but has minimal vascular effects.

LOCAL CONTROL. The need for tissue oxygen delivery, glucose, fatty acids, other nutrients, and many local factors drive local circulatory autoregulation and blood flow. This facilitates blood supply to different tissues and organs, depending on local tissue metabolism.

CLINICAL CONDITIONS AFFECTING ARTERIAL PRESSURE WAVES

Pulse pressure represents the difference between systolic and diastolic pressure. It may be affected by cardiac stroke volume (i.e., the greater the stroke volume output, the more blood pumped into the arterial system and the greater the pulse pressure) and by arterial compliance (i.e., the greater the arterial tree compliance, the less the rise in pressure per stroke volume).

NORMAL PULSE PRESSURE

The pulse pressure is progressively augmented as it is transmitted peripherally by reflection of the pulse wave from peripheral arteries.[70] The clinical significance of this phenomenon is that systolic pressure measured from peripheral arteries may be increased compared with the central aorta, and the diastolic pressure may be comparatively reduced.

ABNORMAL ARTERIAL PULSE PRESSURE

Arterial systolic pressure may be increased when cardiovascular disorders cause greater than normal forward stroke volume, as with patent ductus arteriosus (PDA), arteriovenous fistula, or severe aortic regurgitation (AR). Clinical palpation of the femoral artery may detect a hyperkinetic pulse. Diastolic pressure may decline with conditions causing blood to shunt from aorta to pulmonary artery (PDA); from arterial to venous system (arteriovenous fistula); or aorta back into the left ventricle (AR). Clinical palpation of the femoral artery may detect a wide, "bounding" pulse pressure. Pulse pressures may also be exaggerated with sympathetic hyperactivity, severe bradycardia, and hyperkinetic states associated with severe anemia, fever, or other high-output states such as hyperthyroidism. Reduced amplitude pulse pressures may be detected by femoral arterial palpation when forward cardiac output is reduced, such as with left ventricular outflow obstruction (severe aortic stenosis) or with intravascular volume depletion. Unequal or absent femoral arterial pulse pressures may indicate thrombosis.[80]

PATHOGENESIS OF HYPERTENSION

Diseases that increase cardiac output or total peripheral resistance may result in systemic hypertension (Table 35–4). Heart rate, stroke volume, and cardiac output may increase in hyperdynamic states, in conditions favoring heightened sympathetic activity, or with disorders activating the renin-angiotensin-aldosterone system. Total peripheral resistance may elevate when sodium chloride is retained, in response to increased

TABLE 35–4
Diagnostic Tests for Hypertensive Diseases

Renal Parenchymal Diseases	
Pyelonephritis Chronic interstitial nephritis Polycystic renal disease	CBC; Chemscreen, UA, UC/S, urine protein/creatinine; abdominal radiography/ultrasonography; renal biopsy; arteriography; creatinine clearance
Glomerulonephritis Amyloidosis Glomerulosclerosis	ANA, Coombs' test; serology (*Borrelia, Dirofilaria, Ehrlichia, Babesia*)
Renal Arterial Disease	Renal arteriography, renal vein PRA
Adrenal Diseases	
Hyperadrenocorticism Pituitary-dependent Adrenal neoplasia Iatrogenic	ACTH stimulation test, dexamethasone suppression test
Pheochromocytoma	Plasma/urinary catecholamines; provocative tests*
Hyperaldosteronism	Serum Na^+, K^+, serum aldosterone assay
Thyroid Diseases	
Hyperthyroidism	Serum T_3/T_4; T_3 suppression test
Hypothyroidism	TSH stimulation test; TSH assay
Anemia	1° versus 2°?; reticulocyte count; bone marrow examination
Polycythemia	1° versus 2°?; cardiopulmonary workup; abdominal radiography/ultrasonography; reticulocyte count; erythropoietin assay; bone marrow examination
Hyperviscosity	Chemscreen, protein electrophoresis, bone marrow
↑ Intracranial Pressure	Brain scan (MRI)
Acromegaly	Growth hormone assay; clonidine stimulation test
Hyperestrogenism	Estrogen assay; abdominal ultrasonography

*With pheochromocytoma, phentolamine decreases BP greater than 35/25 mmHg; clonidine does not change BP.

CBC, complete blood count; UA, urinalysis; UC/S, urine culture and sensitivity; ANA, antinuclear antibodies; PRA, plasma renin activity; ACTH, adrenocorticotropic hormone; MRI, magnetic resonance imaging.

levels or sensitivity to catecholamines or angiotensin II. Variable activation of the renin-angiotensin-aldosterone system has been documented in hypertensive cats with chronic renal disease.[80a] Decreased circulating vasodilator concentrations accompanying renal disease may contribute. Heightened sensitivity to vasopressors occurs when increased intracellular (cytosolic) salts such as Na^+ and Ca^{++} predispose to high arteriolar tone. Steroids increase arteriolar sensitivity by several mechanisms that raise intracellular Na^+ and limit depressor systems.[81–84] The total peripheral resistance is also influenced by blood viscosity, which is related to hematocrit, plasma viscosity, and cellular deformability.[62–64] Polycythemia, hypergammaglobulinemia, and red blood cell changes from defective ionic pumps have been associated with hypertension.

It has been suggested that hypertension may be caused by a primary vascular defect involving cationic channels, growth factors, and/or phospholipase C regulation. Many substances cause *in vitro* vascular smooth muscle growth and proliferation, including angiotensin II, catecholamines, vasopressin, growth hormone, insulin, and insulin-like growth factor I, and may therefore contribute to hypertension.[79]

A genetic predisposition described in humans with essential hypertension appears to be polygenetic. It may involve alterations of several macromolecules serving as enzymes, carriers, membrane components, or signal substances. These can affect the structure or function of cellular membranes[85] leading to muscle hypertrophy in response to ordinary loads.

Obese dogs may have higher than normal blood pressure,[4, 14] increased baroreflex sensitivity,[86] and blunted natriuretic responses.[87, 88] These changes may reverse when body weight is normalized.

THE "VICIOUS CYCLE" OF HYPERTENSION

Arteriosclerosis and atherosclerosis decrease arteriolar luminal diameter, decrease arteriolar elasticity, and raise total peripheral resistance. These changes cause a "vicious cycle" by propagating hypertension.

Mechanical smooth muscle stretch caused by elevated blood pressure stimulates Ca^{++} entry through the "stretch-activated channel."[89] This stretch reflex helps maintain increased smooth muscle tone, as occurs in autoregulation. Thus, hypertension itself causes high vascular tone and increased sensitivity to vasopressors.

Vascular remodeling occurs in hypertension. Endothelial cells and platelets produce fibroblast growth factor and platelet-derived growth factor (PDGF), which are mitogenic for smooth muscle cells.[90] Besides the hypertrophy/hyperplasia caused by these growth factors, they activate turnover of membrane phospholipid and phosphatidylinositol and affect phospholipase C activity. In hypertension, platelet phosphatidylinositol 4,5-diphosphate (PIP_2) is decreased, suggesting increased phospholipase C activity. This could explain the increased platelet Ca^{++}, increased sensitivity of platelets to thrombin, serotonin, or collagen (causing release of PDGF), and enhanced Na^+-H^+ exchange seen in human essential hypertensives and in SHR rats.[79]

Nephrosclerosis may also encourage the vicious cycle. As nephrons become hypoxic owing to afferent arteriolar vasoconstriction, the renin-angiotensin-aldosterone system activates. In addition, the diseased kidney may not excrete salt and water efficiently, promoting retention, increased cardiac output, and total peripheral resistance. Lastly, production of vasodilators (prostaglandins, kinins) may be impaired.

CLINICAL CONSEQUENCES OF HYPERTENSION

Hypertension may predispose certain "target" organs to injury, particularly the eyes, kidneys, and cardiovascular and neurovascular systems (Table 35–5). When high systemic blood pressure alters Starling's forces, edema may occur from transudation of fluid and electrolytes; or hemorrhage may result from exudation of plasma proteins or cellular blood components, from microvascular rupture, or from capillary permeability changes. Thus, hypertension should be suspected (1) when signs or evidence of "target" organ injury (e.g., retinal hemorrhage or detachment, epistaxis, or left ventricular hypertrophy) is detected, or (2) when diseases known to predispose to hypertension are diagnosed.

CARDIOVASCULAR CHANGES

Vascular medial hypertrophy or hyperplasia results from increased arterial smooth muscle work induced by vasopressors, high cytosolic Ca^{++}, or autoregulatory vasospasm. High blood pressure also causes intimal damage resulting in arteriosclerosis and atherosclerosis. Arteriosclerosis causes major arteries to become stiff and thickened.

Systemic hypertension and left ventricular hypertrophy are predictors of premature human mortality,[93] but this relationship has not yet been verified in animals. Left ventricular hypertrophy and mass increase from increased afterload, although congestive heart failure is a rare sequela in animals.

TABLE 35–5
Clinical Evidence Suggesting End-Organ Injury in Hypertension

	History, Physical Examination	Clinicopathologic Abnormalities
Cardiac[a]	Gallop rhythm Exercise intolerance Dyspnea Low-grade systolic murmur Arrhythmias Heart failure (rare)	Cardiomegaly Left ventricular hypertrophy Pleural effusion Pulmonary edema
Vascular[b]	Epistaxis	Tortuous aorta Hyaline arteriosclerosis Medial hypertrophy/hyperplasia Fibrinoid necrotizing arteriolitis Atherosclerosis
Ocular[c]	Blindness; retinal hemorrhage/detachment Hyphema; glaucoma (closed-angle) Corneal ulceration Retinal atrophy, hyperreflectivity (old scars)	
Renal[d]	Polyuria/polydipsia (pressure diuresis) Signs of renal failure	Low urine specific gravity (USG) Proteinuria; glomerulosclerosis Tortuous intrarenal vasculature
Cerebrovascular[e]	Head tilt Seizure Paresis, hemiparesis "Stroke"; collapse/coma	Arteriosclerosis CNS hemorrhage Infarction

[a]Dogs, refs. 17, 28, 29, 38, 39, 42, 43, 46–50; cats, refs. 32, 34, 35, 37.
[b]Dogs, refs. 8, 17, 28, 29, 38, 41–45, 49–51; cats, refs. 32, 33.
[c]Dogs, refs. 28, 29, 40, 41, 44, 47, 50, 91, 92; cats, refs. 32–34, 36, 37.
[d]Dogs, refs. 8, 17, 28, 29, 38, 44, 47; cats, refs. 32, 33.
[e]Dogs, ref. 50; cats, refs. 32–34.

INTRAOCULAR CHANGES

Moderate-to-severe hypertension may result in blindness. Lesions include retinal hemorrhage, detachment, and/or hyphema (less frequently, closed-angle glaucoma and corneal ulceration) (Color Plate 2).

RENAL CHANGES

Most hypertensive dogs and cats have polyuria and polydipsia, possibly due to pressure diuresis or primary disease. Arteriosclerosis is associated with glomerulosclerosis (nephrosclerosis). Glomerular atrophy and nephron loss may be seen. Glomerular damage predisposes to proteinuria, and renal failure may be present. Arteriography in hypertensive dogs has shown tortuous intrarenal vasculature suspected to be a secondary change.[28, 47]

CEREBROVASCULAR CHANGES

Central nervous system arteriosclerosis, vasospasm, infarcts, or hemorrhage may cause neurovascular or cerebrovascular accidents (CVAs or "strokes"). Multifocal hemorrhages have been observed in brains of hypertensive cats with neurologic signs.[32, 33]

HISTORY AND PHYSICAL EXAMINATION FINDINGS

SIGNALMENT

Most hypertensive dogs and cats are middle-aged to old (dogs, mean age, 8.9 ± 3.6 years, range, 2 to 14 years;[29] cats, mean age, 15.1 ± 3.8 years, range, 7 to 20 years[32]). The hypertension may be caused by or coincident with geriatric diseases. Older dogs[14, 23, 30] (but not older cats[21]) had higher blood pressure than younger animals. Males may be predisposed,[15, 23, 28–31] and hypertension is linked to the Y-chromosome in SHR rats.[94]

Greyhound dogs have higher blood pressure measurements than other breeds, even if never trained to race.[95] Greyhounds have cardiac hypertrophy (unrelated to pathologic hypertension[96]), relatively high cardiac output with low total peripheral resistance, and greater blood and erythrocyte volume. Their baroreceptors are "set" higher and are more sensitive.[97, 98] These inborn changes are physiologic and do not result in increased morbidity to hypertensive pathology, except for atherosclerosis when the dogs are fed high-fat diets.[11]

Hereditary essential hypertension was reported in a line of Siberian Husky mixed-breed dogs.[48, 99] They

may also have genetic cardiac hypertrophy, possibly inherited separately,[49] and increased platelet aggregation, as in humans with essential hypertension.[100] These changes may be similar to those in the greyhound and represent inbred cardiovascular adaptations favoring endurance.

HISTORY

The history may disclose acute or chronic consequences of end-organ damage, or underlying diseases associated with hypertension. Important clues include polyuria/polydipsia, blindness, epistaxis, signs of congestive heart failure (CHF), kidney failure, hyper- and hypoadrenocorticism, hyper- and hypothyroidism, diabetes, or central neurologic signs. Potential exposure to hypertensive substances should be questioned, including high dietary salt intake,[32, 37] alpha-agonists (e.g., phenylpropanolamine, topical ocular phenylephrine[101]), steroids, lead, cadmium, vitamin D toxicity,[102] nicotine,[103] xylazine,[104] and ketamine.[105]

PHYSICAL EXAMINATION

Complete physical examination should be performed, including ocular examination with direct or indirect ophthalmoscopy (bilateral, but not necessarily symmetric, ocular lesions are common; see Color Plate 2). Neck palpation in elderly cats may reveal thyroid gland nodules. Soft systolic murmurs (grade 2/6) are commonly auscultated in affected dogs (57%[29]) and cats (42%[32]). Abdominal palpation may reveal hepatomegaly from hyperadrenocorticism or small, irregular kidneys. Abdominal distention may be caused by hyperadrenocorticism or protein-losing nephropathy and nephrotic syndrome. Obesity may be present.

DIAGNOSIS AND CHARACTERIZATION OF HYPERTENSION

DOCUMENTATION OF ELEVATED BLOOD PRESSURE

Hypertension is diagnosed when elevated blood pressure is repeatedly recorded over multiple measurements to exclude spuriously elevated readings from fright or excitement. Clinical evidence of end-organ pathology may help support the diagnosis (Table 35–5). In humans, hypertension is defined according to blood pressure measurements that are associated with increased morbidity and mortality, or greater than 160/95 mmHg systolic/diastolic.[2, 105a] There are no such statistics concerning morbidity and mortality in animals.

METHODS OF BLOOD PRESSURE ASSESSMENT

DIRECT BLOOD PRESSURE MEASUREMENT

Direct arterial puncture is the oldest technique and considered the most accurate method for animal blood pressure assessment. Femoral arterial puncture is performed by inserting a 22- to 25-gauge needle connected by heparinized, saline-filled tubing to a physiologic pressure transducer and a hemodynamic oscilloscope-recorder in the nonsedated animal restrained in lateral recumbency.[28, 47] The apparatus can be calibrated with a mercury manometer. Zero baseline balance is performed with the needle held at the same height and angle just before arterial introduction. Less commonly, direct measurements may be recorded from other arteries (carotid loop,[106] external auricular artery,[67] carpal or tarsal arteries). The blood pressure is observed and recorded over multiple cardiac cycles, until it is shown to be "stable" and repeatable. Heart rate is recorded, and observation of the pet's "anxiety" is noted for reference. Sympathetic stimulation will increase the heart rate above normal, and this observation may be helpful in interpreting blood pressure readings.

A disadvantage of this technique is that it requires more physical restraint and induces more pain than noninvasive methods, thereby giving rise to sympathetic stimulation and raised blood pressure.

Hypertension is considered to be present when blood pressure measurements exceed 160/100 mmHg systolic/diastolic using direct arterial puncture in unacclimated animals. This is influenced, however, by technique, method of measurement, and clinical variables. Isolated systolic hypertension (160 to 200 mmHg systolic) may indicate sympathetic activity caused by fright or excitement. Pressures of 220 to 240/130 to 150 mmHg systolic/diastolic have been recorded in hypertensive animals with ocular damage.[28, 29, 32–34] Recordings of 275/170 mmHg have been recorded from a dog with essential hypertension.[47]

INDIRECT (NONINVASIVE) BLOOD PRESSURE MEASUREMENT

The need for rapid, noninvasive blood pressure evaluation has made indirect blood pressure measurement popular. Validation and comparison of indirect with direct techniques in dogs* and cats† have enhanced

*Refs. 4a, 5, 9, 16–18, 53–55, 107.
†Refs. 4a, 20–22, 32, 56–58.

the utility of noninvasive methodologies. Techniques for noninvasive blood pressure include the Doppler,* Dinamap,† plethysmography,[20, 58] xylol indicator,[18] and auscultatory‡ methods. These utilize a cuff to constrict a peripheral artery (on front leg, hind leg, or tail) and a transducer or microphone placed distal to the cuff to detect blood flow or arterial wall motion once the blood pressure overcomes the pressure of the cuff. Various transducers can be used—ultrasonic (Doppler Flow Detector, Parks Medical Electronics Inc, Aloha, OR); oscillometric (Dinamap, Critikon, Tampa, FL); photoplethysmographic (Finapres, Ohmeda, Louisville, CO); or auscultatory audio-amplifiers. The cuff width should be 40 percent of the limb's circumference.[56] Falsely low or high values occur if the cuff is too large or too narrow, respectively.

Simultaneous indirect and direct blood pressure measurements seem to correlate well (cats,[21, 32, 56, 58] dogs[5, 9, 17, 18, 53, 107]), although some studies show that indirect measurements underestimate direct measurements by 7 to 14 mmHg in cats[57] and dogs.[54] In anesthetized cats, the Doppler system placed on the leg was shown to be more efficient, accurate, sensitive, reproducible, and less expensive compared with the Dinamap and Finapres techniques over pressures between 40 mmHg diastolic and 240 mmHg systolic.[58] However, the Doppler technique relies heavily on the subjective interpretation of the observer. This is especially user-dependent for diastolic readings when the Doppler sounds change or become muffled.

Indirect blood pressure monitoring provides a useful clinical screening technique. Normal values are usually less than 160 to 180 mmHg systolic. Hypertensive animals with ocular damage usually have indirect blood pressure of approximately 220 ± 40 mmHg.[32, 34]

CLINICAL ASSESSMENT OF HYPERTENSION

DIAGNOSTIC TESTS

Appropriate diagnostic tests (see Tables 35–4 and 35–5) are required to (1) differentiate essential hypertension from secondary hypertension (i.e., that caused by an underlying disease); (2) reveal end-organ damage; and (3) guide the clinician's choice of anti-hypertension therapy.

*Refs. 4a, 5, 9, 15–17, 20–22, 32, 34, 56–58, 80a, 110a.
†Refs. 4a, 5, 13, 14, 54, 55, 58.
‡Refs. 10–12, 53, 107, 108.

RELATIONSHIP BETWEEN DISEASE AND BLOOD PRESSURE ELEVATION

In humans, the risk of cardiovascular morbidity and mortality increases progressively with increasing blood pressure levels.[109]

Most cats with documented hypertension and end-organ damage have renal disease. However, it is not clear whether renal alterations are a cause or effect, or are coincident with hypertension.[21, 32, 34–36] A few cats with hypertension and end-organ damage had hyperthyroidism.[32, 34] Pheochromocytoma has been reported in a cat, but hypertension was not documented.[110]

Mild hypertension has been documented in dogs with glomerular diseases (80%);[6] other renal abnormalities (61%);[6, 59] hyperadrenocorticism (59 to 100%)[6, 59, 111] and pheochromocytoma (50%);[60] and cats with renal diseases (61 to 65%),[21, 59, 80a, 110a, 155] or hyperthyroidism (87%).[21] Since end-organ damage was not studied, it is unclear how clinically significant mild hypertension is.

MANAGEMENT OF HYPERTENSION

Morbidity and mortality data are lacking for hypertension in dogs and cats. Although when and how to treat is not well established, the rhetorical question, "Is treatment of hypertension beneficial?" is generally answered "Yes" on faith when hypertension is extreme. Additionally, extrapolation from human studies suggests that therapy is beneficial (1) when severe blood pressure elevations are repeatedly recorded, (2) when significant end-organ injury is detected, or (3) in the presence of cardiovascular risk factors. The answer is much less certain for mild degrees of hypertension.

Human antihypertensive therapy involved a "step-care" approach in the 1970s and 1980s. If a first-line drug (often a diuretic or β-blocker) did not lower blood pressure sufficiently, another medication was added, and if necessary a third drug (often a vasodilator) was introduced. Lately, ACE inhibitors and calcium channel blockers have become increasingly popular as first-line antihypertensive drugs.[52, 112, 113] Additional benefits, including regression of left ventricular hypertrophy, have been associated with ACE inhibitors, α- and β-blockers, and calcium channel blocker therapy, but not with diuretics or direct-acting vasodilators (Table 35–6).

THERAPEUTIC GOALS

Considering the practical issues of treatment costs and rigors of daily drug administration, a judicious

TABLE 35-6
Drugs Used for Antihypertensive Therapy in Dogs and Cats

Generic Name (US Trade Name)	Dosage
ACE inhibitors	
Benazepril (Lotensin)	0.25 mg/kg PO q 24 hr
Captopril (Capoten)	0.5–2.0 mg/kg PO q 8–12 hr
Enalapril (Enacard)	0.25–0.75 mg/kg PO q 12–24 hr
Lisinopril (Prinivil)	0.4–1.0 mg/kg PO q 12–24 hr (dogs)
Ramipril (Altace)	0.5 mg/kg PO q 12–24 hr (dogs)
β-Adrenergic receptor blockers	
Atenolol (Tenormin)	6.25–12.5 mg PO q 12 hr (cats) 1.0–2.0 mg/kg PO q 12–24 hr (dogs)
Propranolol (Inderal)	5–10 mg PO q 8–12 hr (cats) 5–80 mg PO q 8–12 hr (dogs)
α-Adrenergic receptor blockers	
Prazosin (Minipress)	0.25–1.0 mg PO q 8–12 hr (cats) 0.25–2.0 mg PO q 8–12 hr (dogs)
Calcium channel blockers	
Amlodipine (Norvasc)	0.625–1.25 mg PO q 24 hr (cats)
Diltiazem (Cardizem)	7.5–15 mg PO q 8–12 hr (cats) 0.5–2.0 mg/kg PO q 8–12 hr (dogs)
Diltiazem (Cardizem CD)	10 mg/kg PO q 24 hr (cats)
Verapamil (Isoptin)	1–2 mg/kg PO q 8–12 hr (cats)
Diuretics	
Hydrochlorothiazide (HydroDiuril)	2–4 mg/kg PO q 12 hr
Furosemide (Lasix)	1–4 mg/kg PO q 8–12 hr
Spironolactone (Aldactone)	2–4 mg/kg PO q 24 hr

philosophy is to (1) validate elevated blood pressure by at least three successive measurements, (2) monitor but do not treat "mild" hypertension, (3) carefully identify and treat secondary conditions known to be associated with hypertension, and (4) base the initial drug choice on patient and disease characteristics.

Individual drug choice(s) depends on (1) hydration status and renal function, (2) heart rate and cardiac function, (3) underlying primary disease, (4) response to therapy, (5) adverse effects, and (6) costs. When beginning drug therapy, low initial doses should be used with the aim of gradual blood pressure reduction while avoiding untoward effects. Animals may vary widely in their response to drugs. No data exist as to how low pressure should be reduced for maximal benefit in animals, and systematic animal studies comparing antihypertensive drugs are currently lacking. In humans, a goal of attaining 140 mmHg systolic and 85 mmHg diastolic is suggested in conjunction with reducing other cardiovascular risk factors.[114]

NONPHARMACOLOGIC THERAPY

When possible, nondrug treatments should constitute initial intervention.[115] These are outlined below.

AVOIDANCE OF DRUGS PROMOTING HYPERTENSION

Exposure to medications known to raise blood pressure should be discontinued. Examples include glucocorticosteroids, phenylpropanolamine, nephrotoxic agents (aminoglycosides, amphotericin, cyclosporine), and amphetamine-like drugs. Glucocorticoids, including topical steroids, should be avoided (systemic effects and pituitary-adrenal axis alterations may result).[116]

WEIGHT CONTROL

Weight reduction is advised for obese animals. Dogs experimentally made overweight developed high blood pressure that dropped when their weight was reduced.[4] Mechanisms include massive natriuresis associated with very low caloric intake,[117] decreased sympathetic activity,[118] and decreased plasma insulin.[119]

DIET MODIFICATION

The role of dietary intervention is unsettled. Rigid sodium restriction was established for hypertensive humans in the late 1940s when few other therapeutic options were available.[120] Severe salt restriction has now been largely discarded in favor of modest sodium reduction, and this appears to be rational for veterinary application as well. In humans, moderate dietary sodium reduction has been shown to lower blood pressure an average of 4.9 ± 1.3 mmHg systolic and 2.6 ± 0.08 mmHg diastolic.[121] Some dogs with essential hypertension have been found to be salt sensitive.[99, 122] Thus, salt restriction in sodium-sensitive individuals should be beneficial.[123] Animals with renal failure and hyperadrenocorticism may retain sodium chloride and water, and salt restriction in hypertensive individuals

may be considered. Whereas some investigators recommend that dietary salt not exceed 0.1 to 0.3 percent Na^+ by dry weight,[124] others argue against specific recommendations regarding sodium restriction.[23] Given available human and animal data, the potential for benefit with remote possibility of harm makes moderate dietary sodium restriction prudent when treatment of moderate-to-severe hypertension is deemed necessary. Since K^+[78] and Mg^{++}[125] salts may help lower blood pressure, these may be considered as salt substitutes. Other Na^+ salts do not seem to raise blood pressure the way sodium chloride does.[126] Therefore, hypertensive animals with renal failure and acidosis may be treated with sodium bicarbonate.

Antihypertensive effects of other nutrients may also have potential relevance. Increased linoleic acid (omega-6 fatty acid from seed oil) in the diet raises renal vasodilatory prostaglandin synthesis. In contrast, dietary linolenic acid (omega-3 fatty acid from linseed oil, olive oil, cod liver oil) inhibits this synthesis and may favor vasoconstriction and hypertension.[127]

TREATMENT OF UNDERLYING MEDICAL DISEASES

Hypertension may regress or disappear with appropriate recognition and treatment of hyperthyroidism.[21, 32] Reversal of obesity may reduce blood pressure in some animals. Other conditions may be less responsive.[28]

PHARMACOLOGIC THERAPY

Many drugs have been advocated to treat systemic hypertension in man. A number of agents have been used in veterinary applications (Table 35–6), although clinical trials to evaluate efficacy are generally lacking.

DIURETICS

A diuretic may be chosen to decrease blood volume and cardiac output if dehydration is not present. Diuretics have been advocated from human studies[128] to treat mild-to-moderate hypertension; they have an advantage of inexpensive cost. Thiazides inhibit sodium and chloride cotransport across the luminal membrane of the early distal convoluted tubule where 5 to 8 percent of filtered sodium is reabsorbed.[129] They are not as effective as loop diuretics. When glomerular filtration is significantly impaired, thiazides (except metolazone) will be ineffective. A few reports describe thiazide use in the dog[28, 47, 50] and cat.[34] Loop diuretics primarily block chloride reabsorption by inhibiting the $Na^+/K^+/Cl^-$ cotransport system of the luminal membrane of the thick ascending limb of Henle's loop, where 35 to 45 percent of filtered sodium is reabsorbed.[130] Therefore, they have greater potency and a more rapid onset of action than do thiazides. Although they are no more effective in lowering blood pressure than are thiazides in humans, they may be effective in the face of severe renal impairment. In hypertensive cats, diuretic therapy was not found to be as effective as β-blockers or ACE inhibitors.[32] Potential side effects of diuretics include acid-base and electrolyte abnormalities, hypovolemia, and dehydration.

ADRENERGIC-INHIBITING DRUGS

Based upon pharmacologic properties, adrenergic receptors are subdivided into three major groups: (1) β-receptors (which couple to stimulatory G proteins to activate adenyl cyclase), (2) α_1-receptors (which couple to other G proteins to activate synthesis of the second messenger, inositol triphosphate and diacylglycerol), and (3) α_2-receptors (which couple to inhibitory G proteins to inhibit adenyl cyclase).[131] These receptors mediate various sympathetic nervous system and cardiovascular actions. Additionally, specific receptors distinct from α-adrenergic receptors have been identified and designated as imidazoline receptors (their activation by imidazoline causes a hypotensive effect), although drugs susceptible to being recognized by imidazoline receptors are capable of being recognized by α_2-receptors.[132] Accordingly, a number of drugs act as antagonists (used mostly in veterinary medicine) or agonists to block or occupy α- or β-receptor sites on effector cells.

BETA-ADRENERGIC RECEPTOR BLOCKERS. The β-blockers rival diuretics as the most frequently used class of drugs in human antihypertensive therapy, and they are used in hypertensive dogs[28, 47] and cats.[32, 34, 37] They affect a number of physiologic functions that regulate blood pressure,[133, 134] including reducing heart rate, contractility, and thus cardiac output; diminishing renin secretion; potentially decreasing central sympathetic nervous outflow; and inhibiting catecholamine release by presynaptic blockade. Clinical selection may be influenced by pharmacologic differences between β-blocker agents. Lipophilic drugs (propranolol, metoprolol) have high first-pass hepatic metabolism and thus less bioavailability. Lipophobic agents (atenolol, nadolol) are mainly excreted unchanged by the kidney, have a longer half-life, and may cause fewer CNS side effects.[135] All β-blockers competitively antagonize cardiac β_1-receptors but vary in their β_2-receptor blockade (i.e., vessels, bronchi, endocrine organs). However, there may be few antihypertensive differences between agents having greater (e.g., atenolol, metoprolol) compared with weaker (e.g., propranolol) cardioselective properties.[136] The cardioselective β_1-blocker atenolol seems to have the advantage of once-daily administra-

tion in many animals, compared with propranolol (given every 8 to 12 hours). Compliance can easily be monitored with β-blockers, since heart rate should decrease markedly from pretreatment baseline values when the drug is being administered. For example, cats receiving 12.5 mg of atenolol daily or 5 mg of propranolol tid should have resting heart rates of between approximately 120 and 150 beats/minute. Potential side effects include bradycardia, CNS depression, glucose intolerance, bronchospasm, and hypotension. There have been few clinical veterinary trials. In one study, propranolol was ineffective as long-term monotherapy in treating hypertensive cats.[80a]

ALPHA-ADRENERGIC RECEPTOR BLOCKERS. Two types of α-receptors have been defined: presynaptic α_2-receptors, which modulate neurotransmitter activity through negative feedback mechanisms that inhibit catecholamine release from nerve endings when these receptors are occupied by norepinephrine; and post-synaptic α_1-(vascular) receptors. Prazosin blocks α_1-receptor activation by circulating or neurally released catecholamines (which normally induces vasoconstriction). This blockade dilates resistance vessels, which reduces peripheral resistance without major changes in cardiac output. Presynaptic α_2-receptors remain capable of binding neuronally released norepinephrine (neurotransmitter), inhibiting the latter's own release and preventing, by direct negative feedback, development of reflex tachycardia and a rise in plasma renin.[133] Antihypertensive efficacy may be limited if plasma norepinephrine increases when blood pressure falls, owing to a baroreceptor-mediated increase in plasma norepinephrine.[137]

Prazosin has been effectively combined with diuretics or β-blockers in humans and has been effective in chronic renal failure. Tachyphylaxis to its antihypertensive action has been reported not to be a problem in human studies,[138] although it is ineffective in chronic heart failure management.[139]

DRUGS BLOCKING BOTH α- AND β-RECEPTORS. Labetalol, a lipid-soluble drug, is a nonselective β_1- and β_2-receptor blocker and is highly selective for α_1-receptors. In humans, it reduces blood pressure by decreasing peripheral vascular resistance, with little effect on cardiac output.[140] Clinical veterinary use has been limited.

VASODILATORS

Various classification schemes for vasodilators have been proposed. Those entering vascular smooth muscle to cause vasodilation have been termed "direct vasodilators," whereas drugs acting by other mechanisms have been called "indirect vasodilators." The latter (e.g., ACE inhibitors, calcium-entry blockers, α-receptor–mediated blockers) are described according to their cellular site of action or signal mechanism.

Hydralazine has become a third-line agent (after diuretics and β-blockers) in humans. It acts directly to relax vascular smooth muscle of peripheral arterioles, decreasing peripheral vascular resistance and blood pressure. A baroreceptor-mediated reflex enhancing sympathetic discharge usually increases heart rate, stroke volume, and cardiac output coincident with vasodilation.[141] Nitrates, particularly intravenous sodium nitroprusside, are used in the uncommon situation when hypertensive crisis is encountered (i.e., situations in which immediate blood pressure reduction is needed, such as hypertensive encephalopathy).

ALPHA-ADRENERGIC RECEPTOR AGONIST DRUGS

Drugs acting at the α_2-receptor exert their antihypertensive effect by activating peripheral neuronal presynaptic α_2-receptors to reduce norepinephrine release, and by directly activating postsynaptic CNS receptors, resulting in decreased sympathetic tract outflow activity. Agents such as clonidine and methyldopa have had little clinical use in veterinary medicine, however.

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

These drugs lower blood pressure by inhibiting circulating levels of angiotensin II.[142] The mechanism involves inhibiting ACE, which normally converts the inactive decapeptide angiotensin I to the potent vasoconstrictor angiotensin II. Additional effects likely contribute to antihypertensive actions. These include decreased aldosterone secretion reducing renal sodium retention,[143] increased vasodilatory prostaglandin synthesis,[144] or direct inhibition of vascular hypertrophy.[145] In addition, ancillary effects of ACE inhibitors (ACEI) may include beneficial cardiovascular actions (salutary effects on ventricular remodeling and regression of hypertrophy); maintain cerebral blood flow; and protect renal function (e.g., preferential efferent renal arteriolar dilation following reduction of circulating angiotensin II increases renal blood flow while reducing intraglomerular pressure).[146]

Monotherapy using ACEI drugs is often chosen for initial management of mild-to-moderate human hypertension, especially if there is proteinuria or heart failure.[128] Enalapril, benazopril, lisinopril, ramipril, and captopril are ACEIs used in veterinary medicine. Comparison of efficacy and safety has not been studied, but enalapril has been found to be safe when used in dogs with heart failure.[147, 148] Clinical trials evaluating ACEIs for hypertension are limited. In one study, enalapril provided effective long-term monotherapy in one of six cats with hypertension associated with chronic renal

disease.[80a] A combination with low doses of diuretics or β-adrenergic blockers may enhance ACEI efficacy and thus, should be contemplated before raising ACEI dosage. The tolerated dose of ACEIs may be higher when they are used as antihypertensive agents in the absence of heart failure and renal insufficiency, or in combination with diuretics.[28, 32, 37, 44, 47] The greatest risk is development of functional renal insufficiency, potentially leading to progressive renal failure, especially when concomitant diuretic therapy is administered or if heart failure is present. Vomiting, diarrhea, and hypotension are also potential side effects.[149]

CALCIUM CHANNEL BLOCKERS

These drugs lower blood pressure by interfering with calcium-dependent contractions of vascular smooth muscle, thereby reducing peripheral vascular resistance.[150] They may also decrease vascular responsiveness to angiotensin II. A number of agents are available, differing with respect to sites and modes of action on slow calcium channels, cardiovascular activity, duration of action, and side effects. First-generation agents (verapamil, nifedipine, diltiazem) possess varying side effects related to vasodilation, depressed cardiac conduction, and contractility. Verapamil exhibits both marked arteriolar dilation as well as direct negative inotropic action and depresses atrioventricular conduction with greater effect on the AV node (versus diltiazem, which affects sinoatrial nodal conduction more). Since verapamil undergoes substantial first-pass metabolism in the liver, drugs or conditions that reduce hepatic blood flow or liver enzyme function prolong its elimination. Half-life for elimination in dogs and cats varies between 1 and 5 hours.[151] Diltiazem produces hemodynamic and electrophysiologic effects similar to those of verapamil, with a comparable half-life in dogs, but it causes less myocardial depression and undergoes less first-pass hepatic metabolism. In cats, a mean bioavailability of 94 percent and an elimination half-life of 2 hours were recorded (approximately 38% and 7 hours, respectively, for long-acting diltiazem CD).[152] Nifedipine is a potent arteriolar dilator but has been little used in veterinary medicine to date. Newer second-generation calcium channel blockers such as amlodipine exhibit more peripheral vasodilation with fewer effects on heart rate or contractility.

Calcium blockers have become one of the standard first-line treatments for essential hypertension in humans. Careful monitoring is advised when combining diltiazem or verapamil with a β-adrenergic blocker because of the potential adverse effects on cardiac conduction.[153] Contraindications include second- or third-degree AV block, hypotensive states, and myocardial failure. Side effects include vomiting, diarrhea, and hypotension. Verapamil has potent negative inotropic and chronotropic effects and is infrequently used in animals. Anorexia, lethargy, and vomiting were seen with verapamil at 1 mg/lb (2 mg/kg) every 8 hours; 0.5 mg/lb (1 mg/kg) every 12 hours did not lower blood pressure measurements.[44] Even less experience is available for nifedipine, which has great peripheral vasodilator effects. Diltiazem is relatively safe in dogs and cats, having fewer inotropic and chronotropic effects than has verapamil. Amlodipine administered once daily (0.625–1.25 mg) as a monotherapy agent for treating cats with systemic hypertension appears to be safe and effective.[110a, 154–155a]

HYPERTENSIVE EMERGENCIES

Although uncommon, hypertensive emergencies occur. These are typically heralded by the clinical sign of acute blindness, neurologic signs (especially encephalopathy, cerebrovascular events), or occasionally malignant renal disease. The goal of therapy is blood pressure reduction to levels that ameliorate clinical signs. Re-establishment of normal blood pressure is achieved by chronic oral therapy. A precipitous drop in blood pressure can cause hypotension, cerebral ischemia, and neurologic signs, and thus should be avoided.[156, 157] In dogs, β-blockers (propranolol, 5 to 40 mg orally tid) or vasodilators (hydralazine, 1.0 to 2.0 mg/kg orally bid, or prazosin, 1 to 2 mg orally bid-tid) may be first-choice agents. In cats, the calcium channel blocker amlodipine (0.625 mg orally daily), the β-blocker propranolol (2.5 to 7.5 mg orally tid), or atenolol (6.25 to 12.5 mg orally sid-bid) can be selected. Animals with severe clinical signs or who have not responded to these drugs may receive, under scrutiny of continuous blood pressure monitoring, sodium nitroprusside (start at 0.5 to 1 μg/kg/min, constant rate infusion, titrate to effect, usually a maximum of 5 μg/kg/min [beware of cyanide toxicity in cats]) or the ultra-short acting β-blocker esmolol (500 μg/kg/min intravenously slowly to load; 50 to 250 μg/kg/min, constant rate infusion, to effect [beware of bradycardia, heart block, negative inotropism]).

PATIENT MONITORING

Surveillance of the hypertensive animal is important whether or not treatment is administered. This includes repeated blood pressure measurements, physical examinations, diagnostic tests individualized to detect end-organ changes, and monitoring for side effects associated with therapy. Initially, repeat examinations may be required every 1 to 2 weeks until the animal is stable. Thereafter, evaluation is dictated by clinical status.

Animals taking antihypertensive medications may not be able to autoregulate well, especially if they have significant systemic or metabolic disease. Care must therefore be taken to avoid or treat related complications such as hypotension, dehydration, anorexia, or use of hypotensive anesthetics.[157]

PROGNOSIS

The prognosis depends on the cause of the hypertension and the extent of end-organ damage. Animals with essential hypertension may live many years. Vision may improve if the onset of blindness was acute, but renal function often does not get better and may deteriorate, especially in dogs who present with azotemia.[28] Many cats with systemic hypertension can be well managed with amlodipine.[32, 80a, 110a, 154–155a] Dogs with hyperadrenocorticism and cats with hyperthyroidism generally do well with treatment of the underlying disease and, if necessary, antihypertensive drug administration. Dogs with essential hypertension have been maintained for years without renal compromise.[28, 47, 48]

REFERENCES

1. Kaplan NM. Hypertension: Prevalence, risks, and effect of therapy. Ann Intern Med 98:705, 1983
2. Zanchetti A. What blood pressure level should be treated? *In* Laragh LH, Brenner BM (eds): Hypertension: Pathophysiology, Diagnosis, and Management. New York, Raven Press, 1990, p 1967
3. Mancia G, Bertinieri G, Grassi G, et al. Effects of blood pressure measurement by the doctor on patient's blood pressure and heart rate. Lancet 2(8352):695, 1983
4. Rocchini AP, Moorehead C, Wentz E, et al. Obesity-induced hypertension in the dog. Hypertension 9(Suppl III):III-64, 1987

4a. Wagner AE, Brodbelt MA. Arterial blood pressure monitoring in anesthetized animals. J Am Vet Assoc 210:1279, 1997

5. Chalifoux A, Dallaire A, Blais D, et al. Evaluation of the arterial blood pressure of dogs by two noninvasive methods. Can J Comp Med 49:419, 1985
6. Kallett AJ, Cowgill LD. Hypertensive states in the dog. Scientific Proceedings, American College of Veterinary Internal Medicine, 1982, p 79
7. Lupu AN, Maxwell MH, Kaufman JJ, et al. Experimental unilateral renal artery constriction in the dog. Circ Res 30:567, 1972
8. Anderson LJ, Fisher EW. The blood pressure in canine interstitial nephritis. Res Vet Sci 9:304, 1968
9. Freundlich JJ, Detweiler DK, Hance HE. Indirect blood pressure determination by the ultrasonic Doppler technique in dogs. Curr Ther Res 14:73, 1972
10. Wakerlin GE. Normotension and hypertension in the dog. J Am Vet Med Assoc 102:346, 1943
11. Detweiler DK, Trautvetter E. Hypertension in dogs, incidence and clinical significance. Kleintierpraxis 25:227, 1980
12. Shingatgeri MK, Nambiar KTK, Govindan Nayar KN. A preliminary report on the use of a modified compression cuff to fit the sphygmomanometer in determining arterial blood pressure in dogs. Indian Vet J 40:770, 1963
13. Edwards NJ. Non-invasive blood pressure measurements in the clinical setting. Proceedings, 8th Annual Veterinary Medicine Forum, 1990, p 273
14. Coulter DB, Keith JC. Blood pressures obtained by indirect measurement in conscious dogs. J Am Vet Med Assoc 184:1375, 1984
15. Knight DH, Riffle RA, Melbin J. Distribution of blood pressure in Beagle dogs as determined by a Doppler ultrasound technique. Fed Proc 34:399, 1975
16. Remillard RL, Ross JN, Eddy JB. Variance of indirect blood pressure measurements and prevalence of hypertension in clinically normal dogs. J Am Vet Res 52:561, 1991
17. Weiser MG, Spangler WL, Gribble DH. Blood pressure measurement in the dog. J Am Vet Med Assoc 171:354, 1977
18. Wilson RB, Clarke TJ. Indirect measurement of systolic blood pressure in dogs by the use of xylol pulse indicator. J Am Vet Med Assoc 144:981, 1964
19. Gordon DB, Goldblatt H. Direct percutaneous determination of systemic blood pressure and production of renal hypertension in the cat. Proc Soc Exp Biol Med 125:177, 1967
20. Mahoney LT, Brody MJ. A method for indirect recording of arterial pressure in the conscious cat. J Pharm Meth 1:61, 1978
21. Kobayashi DL, Peterson ME, Graves TK, et al. Hypertension in cats with chronic renal failure or hyperthyroidism. J Vet Intern Med 4:58, 1990
22. Klevans LR, Hirkaler G, Kovacs JL. Indirect blood pressure determination by Doppler technique in renal hypertensive cats. Am J Physiol 237:H720, 1979
23. Bodey AR. Systemic hypertension in the dog—fact or fiction? Proceedings, 18th Annual Waltham/OSU Symposium: Cardiology. Vernon, CA, 1994, p 46
24. National Center for Health Statistics. *In* Rowland W, Roberts J (eds): Blood pressure levels and hypertension in persons aged 6–74 years: United States, 1976–1980. Advance data from vital and health statistics. No. 84, DHHS Pub. No. (PHS) 82–1250. Hyattsville, MD, Public Health Service, October 8, 1982
25. Kaplan NM. Systemic hypertension. *In* Braunwauld E (ed): Heart Disease. 4th ed. Philadelphia, WB Saunders, 1992, p 852
26. Grundy SM, Greenland P, Herd A, et al. Cardiovascular and risk factor evaluation of healthy American adults. Circulation 75:1340A, 1987
27. Kannel WB, Sorlie P. Hypertension in Framingham. *In* Paul O (ed): Epidemiology and Control of Hypertension. Miami, Symposia Specialists, 1975, p 553
28. Littman MP, Robertson JL, Bovée KC. Spontaneous systemic hypertension in dogs: Five cases (1981–1983). J Am Vet Med Assoc 193:486, 1988
29. Littman MP. Spontaneous systemic hypertension in dogs; Abstract. Sci Proc Br Small Anim Vet Assoc Congress, 1991, p 119
30. Valtonen MH, Oksanen A. Cardiovascular disease and nephritis in dogs. J Small Anim Pract 13:687, 1972
31. Doursout MF, Chelly JE, Wouters P, et al. Effect of gender in centrally induced angiotensin II hypertension in dogs. Hypertension 15(Suppl 2):I117, 1990

32. Littman MP. Spontaneous systemic hypertension in 24 cats. J Vet Intern Med 8:79, 1994
33. Littman MP. Cerebrovascular accidents in cats with spontaneous systemic hypertension; Abstract. Br Small Anim Vet Assoc (BSAVA) Congress, 1991, p 156
34. Morgan RV. Systemic hypertension in four cats: Ocular and medical findings. J Am Anim Hosp Assoc 22:615, 1986
35. Lesser M, Fox PR, Bond BR. Assessment of hypertension in 40 cats with left ventricular hypertrophy by Doppler-shift sphygmomanometry. J Small Anim Pract 33:55, 1992
36. Stiles J, Polzin DJ, Bistner SI. The prevalence of retinopathy in cats with systemic hypertension and chronic renal failure or hyperthyroidism. J Am Anim Hosp Assoc 30:564, 1994
37. Turner JL, Brogdon JD, Lees GE, et al. Idiopathic hypertension in a cat with secondary hypertensive retinopathy associated with a high-salt diet. J Am Anim Hosp Assoc 26:647, 1990
38. Hamilton WF, Pund ER, Slaughter RF, et al. Blood pressure values in street dogs. Am J Physiol 128:233, 1940
39. Katz JI, Skom JH, Wakerlin GE. Pathogenesis of spontaneous and pyelonephritic hypertension in the dog. Circ Res 5:137, 1957
40. Rubin LF. Atlas of Veterinary Ophthalmoscopy. Philadelphia, Lea & Febiger, 1974, pp 110, 132
41. Rubin LF. Ocular manifestations of arteriosclerosis and hypertension in dogs. Proc Am Coll Vet Ophthalmol 6:56, 1975
42. McIntyre WIM, Montgomery GL. Renal lesions in *Leptospira canicola* infection in dogs. J Pathol Bacteriol 64:145, 1952
43. Stamler J, Katz LN, Rodbard S. Serial renal clearances in dogs with nephrogenic and spontaneous hypertension. J Exp Med 90:511, 1949
44. Paulsen ME, Allen TA, Jaenke RS, et al. Arterial hypertension in two canine siblings: Ocular and systemic manifestations. J Am Anim Hosp Assoc 25:287, 1989
45. Gwin RM, Gelatt KN, Terrall TG, et al. Hypertensive retinopathy associated with hypothyroidism, hypercholesterolemia, and renal failure in a dog. J Am Anim Hosp Assoc 14:200, 1978
46. Breitschwerdt EB, Turk MAM, Glaze MB, et al. Chronic azotemia and hypertension in two Bluetick Coonhound siblings. Comp Cont Ed 8:487, 1986
47. Bovée KC, Littman MP, Crabtree BJ, et al. Essential hypertension in a dog. J Am Vet Med Assoc 195:81, 1989
48. Tippett FE, Padgett GA, Eyster G. Primary hypertension in a colony of dogs. Hypertension 9:49, 1987
49. Bovée KC, Douglas PS. Abnormal left ventricular shape and function in hypertensive dogs. J Vet Intern Med 4:117, 1990
50. Blanchard GL, Eyster GE, Carrig CB, et al. Primary essential hypertension in a Siberian Husky dog. Fed Proc 38:1350, 1979
51. Dhupa N, Littman P. Epistaxis. Comp Cont Ed 14: 1033, 1992
52. Williams GH. Hypertensive vascular disease. *In* Wilson JD, Braunwald E, Isselbacher KJ, et al. (eds): Harrison's Principles of Internal Medicine. New York, McGraw-Hill, 1991, p 1001
53. Wessale JL, Smith LA, Reid M, et al. Indirect auscultatory systolic and diastolic pressures in the anesthetized dog. Am J Vet Res 46:2129, 1985
54. Hunter JS, McGrath CJ, Thatcher CD, et al. Adaptation of human oscillometric blood pressure monitors for use in dogs. Am J Vet Res 51:1439, 1990
55. Vincent IC, Michell AR, Leahy RA. Noninvasive measurement of arterial blood pressure in dogs: A potential indicator for the identification of stress. Res Vet Sci 54:195, 1993
56. McLeish I. Doppler ultrasonic arterial pressure measurement in the cat. Vet Rec 100:290, 1977
57. Grandy JL, Dunlop CI, Hodgson DS, et al. Evaluation of the Doppler ultrasonic method of measuring systolic arterial blood pressure in cats. Am J Vet Res 53:1166, 1992
58. Binns SH, Sisson D, Buscio DA, et al. Doppler ultrasonographic oscillometric sphygmomanometric, and photoplethysmographic techniques for noninvasive blood pressure measurement in anesthetized cats. J Vet Intern Med 9:405, 1995
59. Ross LA. Hypertensive disease. *In* Ettinger SJ (ed): Textbook of Veterinary Internal Medicine. 3rd ed. Philadelphia, WB Saunders, 1989, p 2047
60. Twedt DC, Wheeler SL. Pheochromocytoma in the dog. Vet Clin North Am 14:767, 1984
61. Berne RM, Levy MN. Hemodynamics. *In* Berne RM, Levy MN (eds): Physiology. 2nd ed. St Louis, CV Mosby, 1988
62. Chabanel A, Chien S. Blood viscosity as a factor in human hypertension. *In* Laragh JH, Brenner BM (eds): Hypertension: Pathophysiology, Diagnosis, and Management. New York, Raven Press, 1990, p 329
63. Levi E, Baskurt OK, Dikmenoglu N, et al. Effect of erythrocyte deformability on renal hemodynamics and plasma renin activity. Am J Nephrol 12:37, 1992
64. Tsuda K, Shima H, Takeda J, et al. The role of endogenous Na^+, K^+-adenosine triphosphatase inhibitory factor in the regulation of membrane fluidity of erythrocytes in essential hypertension. J Hypertens 10:657, 1992
65. Bovée KC, Papanek PE, Skelton MM, et al. Lability of blood pressure in genetically hypertensive dogs using 24-hour monitoring. J Vet Intern Med 6:116, 1992
66. Martin J, Sutherland CJ, Zbrozyna AW. Habituation and conditioning of the defense reactions and their cardiovascular components in cats and dogs. Pflugers Arch 365:37, 1976
67. Kutz SA, Detweiler DK, Cimprich RE, et al. Evaluation of a direct blood pressure measurement technique for canine toxicity studies. Fundam Appl Toxicol 5:391, 1985
68. Engeland WC, Miller P, Gann DS. Pituitary-adrenal and adrenomedullary responses to noise in awake dogs. Am J Physiol 258:R672, 1990
69. Little RC. Physiology of the Heart and Circulation. 3rd ed. Chicago, Year Book, 1985, p 329
70. Guyton AC. Textbook of Medical Physiology. 8th ed. Philadelphia, WB Saunders, 1991
71. Franklin SS, Weber MA. Measuring hypertensive cardiovascular risk: The vascular overload concept. Am Heart J 128:793, 1994
72. Pranzatelli MR, DeVivo DC. The role of the central nervous system in blood pressure regulation. *In* Loggie JMH (ed): Pediatric and Adolescent Hypertension. Oxford, Blackwell Scientific, 1992, p 53
73. Niarchos AP, Pickering TG, Case DB, et al. Role of renin-angiotensin system in blood pressure regulation: The cardiovascular effects of converting enzyme inhibition in normotensive subjects. Circ Res 45:829, 1979
74. Dzau VJ, Burt DW, Pratt RE. Molecular biology of the renin-angiotensin system. Am J Physiol 255:F563, 1988

75. Guyton AC, Hall JE, Coleman TG, et al. The dominant role of the kidneys in long-term arterial pressure regulation in normal and hypertensive states. *In* Laragh JH, Brenner BM. Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York, Raven Press, 1995, p 1211
76. Blaustein MP. Sodium ions, calcium ions, blood pressure regulation, and hypertension: A reassessment and a hypothesis. Am J Physiol 232:C165, 1977
77. Nicholson JP, Resnick LM, Cigarroa J. The pressor effect of sodium-volume expansion is calcium mediated. Am J Hypertens 4:904, 1991
78. Tobian L. The protective effects of high-potassium diets in hypertension, and the mechanisms by which high-NaCl diets produce hypertension—a personal view. *In* Laragh JH, Brenner BM (eds): Hypertension; Pathophysiology, Diagnosis, and Management. New York, Raven Press, 1990, p 49
79. Meyer P. Similarities in cellular proliferative mechanisms in hypertension and neoplasia. *In* Laragh JH, Brenner BM (eds): Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York, Raven Press, 1995, p 299
80. Braunwald E. The physical examination. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB Saunders, 1992, p 21
80a. Jensen J, Henik RA, Brownfield M, et al. Plasma renin activity and angiotensin I and aldosterone concentrations in cats with hypertension associated with chronic renal disease. Am J Vet Res 58:535, 1997
81. Nakamoto H, Suzuki H, Kagayama Y, et al. Depressor systems contribute to hypertension induced by glucocorticoid excess in dogs. J Hypertens 10:561, 1992
82. Nakamoto H, Suzuki H, Kagayama Y, et al. Characterization of alterations of hemodynamics and neuroendocrine hormones in dexamethasone-induced hypertension in dogs. Clin Exp Hypertens [A] 13:587, 1991
83. Saruta T, Suzuki H, Handa M, et al. Multiple factors contribute to the pathogenesis of hypertension in Cushing's syndrome. J Clin Endocrinol Metab 62:275, 1986
84. Lohmeier TE, Kastner PR. Chronic effects of ACTH and cortisol excess on arterial pressure in normotensive and hypertensive dogs. Hypertension 4:652, 1982
85. Folkow B. The structural factor in hypertension: With special emphasis on the altered geometric design of the systemic resistance arteries. *In* Laragh JH, Brenner BM (eds): Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York, Raven Press, 1995, p 481
86. Wehberg KE, West DB, Kieswetter C, et al. Baroreflex sensitivity in the canine model of obesity-induced hypertension. Am J Physiol 259:R981, 1990
87. West DB, Wehberg KE, Kieswetter K, et al. Blunted natriuretic response to an acute sodium load in obese hypertensive dogs. Hypertension 19 (Suppl 1):I96, 1992
88. Hall JE, Brands MW, Dixon WN, et al. Obesity-induced hypertension: Renal function and systemic hemodynamics. Hypertension 22:292, 1993
89. Khalil RA, van Breemen C. Calcium mobilization and homeostasis in vascular smooth muscle and their relevance to hypertension. *In* Laragh JH, Brenner BM (eds): Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York, Raven Press, 1995, p 523
90. Schwartz SM, Majesky MW, Dilley RJ. Vascular remodeling in hypertension and atherosclerosis. *In* Laragh JH, Brenner BM (eds): Hypertension: Pathophysiology, Diagnosis, and Management. New York, Raven Press, 1990, p 521
91. Mertz BP, Pfister R, Brueckner R, et al. Rhegmatogenous retinal detachment in a hypertensive dog. Lens Eye Toxic Res 7:67, 1990
92. Preiswerk G, Breitenfeld K. Examination of the eye of renal hypertensive dogs. Experientia 40:458, 1984
93. Casale PN, Devereux RB, Milner M, et al. Value of left ventricular measurements of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. Ann Intern Med 105:173, 1986
94. Ely DL, Turner ME. Hypertension in the spontaneously hypertensive rat is linked to the Y chromosome. Hypertension 16:277, 1990
95. Detweiler DK, Cox RH, Alonso R, et al. Characteristics of the Greyhound cardiovascular system. Fed Proc 34:399, 1975
96. Cohen MV. Coronary vascular reserve in the greyhound with left ventricular hypertrophy. Cardiovasc Res 20:182, 1986
97. Detweiler DK, Cox RH, Alonso R, et al. Hemodynamic characteristics of the young adult Greyhound. Fed Proc 33:360, 1974
98. Cox RH, Bagshaw RJ, Detweiler DK. Baroreceptor reflex cardiovascular control in mongrel dogs and racing greyhounds. Am J Physiol 249:H655, 1985
99. Bovée KC, Littman MP, Saleh F, et al. Essential hypertension in dogs: A new animal model. J Hypertens (Suppl 5) 4:S172, 1986
100. Thomas JS, McConnell MF, Saleh F, et al. Platelet aggregation and dense granule secretion in a colony of dogs with spontaneous hypertension. J Hypertens 10:1493, 1992
101. Pascoe PJ, Ilkiw JE, Stiles J, et al. Arterial hypertension associated with topical ocular use of phenylephrine in dogs. J Am Vet Med Assoc 205:1562, 1994
102. Spangler WL, Gribble DH. Experimental vitamin D toxicity and hypertension in the dog. Vet Pathol 12:66, 1975
103. Vig MM. Nicotine poisoning in a dog. Vet Hum Toxicol 32:573, 1990
104. Hsu WH, Lu ZX, Hembrough FB. Effect of xylazine on heart rate and arterial blood pressure in conscious dogs, as influenced by atropine, 4-aminopyridine, doxapram, and yohimbine. J Am Vet Med Assoc 186:153, 1985
105. Middleton DJ, Ilkiw JE, Watson ADJ. Physiologic effects of thiopentone, ketamine and CT 1341 in cats. Res Vet Sci 32:157, 1982
105a. Alderman MH, Marantz PR. Clinical trials as a guide to intervention. *In* Laragh JH, Brenner BM (eds): Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York, Raven Press, 1995, p 2487
106. O'Brien DJ, Chapman WH, Rudd FV, et al. Carotid loop method of blood pressure measurement in the dog. J Appl Physiol 30:161, 1971
107. Ferris HW, Hynes JF. Indirect blood pressure readings in dogs: Description of method and report of results. J Lab Clin Med 16:597, 1931
108. Allen FM. Auscultatory estimation of the blood pressure of dogs. J Metabol Res 4:431, 1923
109. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1: Prolonged differences in blood pressure: Prospective observational studies corrected for the regression dilution bias. Lancet 335:765, 1990
110. Patnaik AK, Erlandson RA, Lieberman PH, et al. Extra-adrenal pheochromocytoma (paraganglioma) in a cat. J Am Vet Med Assoc 197:104, 1990

110a. Henik RA, Snyder PS, Volk LM. Treatment of systemic hypertension in cats with amlodipine besylate. J Am Vet Med Assoc 33:226, 1997
111. Ortega T, Feldman E, Cowgill L, et al. Evaluation of arterial blood pressure (BP) and urine protein/creatinine ratio (UP/C) in dogs with canine Cushing's syndrome (CCS). J Vet Intern Med 8:164, 1994
112. Houston MC. New insights and new approaches for the treatment of essential hypertension: Selection of therapy based on coronary heart disease risk factor analysis, hemodynamic profiles, quality of life, and subsets of hypertension. Am Heart J 117:911, 1989
113. The 1988 report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. Arch Intern Med 148:1023, 1988
114. Kaplan NM. Treatment of hypertension: Rationale and goals. *In* Clinical Hypertension. Baltimore, Williams & Wilkins, 1994, p 145
115. Stamler R, Stamler J, Grimm R, et al. Nutritional therapy for high blood pressure. J Am Med Assoc 257:1484, 1987
116. Glaze MB, Crawford MA, Nachreiner RF, et al. Ophthalmic corticosteroid therapy: Systemic effects in the dog. J Am Vet Med Assoc 192:73, 1988
117. Krieger DR, Landsberg L. Neuroendocrine mechanisms in obesity-related hypertension. *In* Laragh JH, Brenner BM, Kaplan NM (eds): Perspectives in Hypertension. Vol 2: Endocrine Mechanisms in Hypertension. New York, Raven Press, 1989, p 105
118. Anderson B, Elam M, Wallin BG, et al. Effect of energy restricted diet on sympathetic muscle nerve activity in obese women. Hypertension 18:783, 1991
119. Franssila-Kallunki A, Rissanen A, Ekstrand A, et al. Effects of weight loss on substrate oxidation, energy expenditure, and insulin sensitivity in obese individuals. Am J Clin Nutr 55:356, 1992
120. Kempner W. Treatment of hypertensive vascular disease with rice diet. Am J Med 4:545, 1948
121. Cutler JA, Follman D, Elliot P, et al. An overview of randomized trials of sodium reduction and blood pressure. Hypertension 17(Suppl 1):27, 1991
122. Bovée KC. Variance of blood pressure response to oral sodium intake in hypertensive dogs. J Vet Intern Med 4:126, 1990
123. Kaplan N. Systemic hypertension therapy. *In* Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB Saunders, 1992, p 852
124. Cowgill LD, Kallett AJ. Recognition and management of hypertension in the dog. *In* Kirk RW (ed): Current Veterinary Therapy VIII. Philadelphia, WB Saunders, 1983, p 1025
125. Harlan WR, Harlan LC. Blood pressure and calcium and magnesium intake. *In* Laragh JH, Brenner BM (eds): Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York, Raven Press, 1995, p 1143
126. Kurtz TW, Morris RC Jr. Dietary chloride as a determinant of "sodium-dependent" hypertension. Science 222:1139, 1983
127. Iacono JN, Dougherty RM. Blood pressure and fat intake. *In* Laragh JH, Brenner BM (eds): Hypertension: Pathophysiology, Diagnosis, and Management. New York, Raven Press, 1990, p 257
128. Joint National Committee. The fifth report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure (JNC V). Arch Intern Med 153:154, 1993
129. Rose BD. Diuretics. Kidney Int 39:336, 1991
130. Boles Ponto LL, Schoenwald RD. Furosemide (frusemide): II. A pharmacokinetic/pharmacodynamic review. Clin Pharmacokinet 18:460, 1990
131. Strasser RH, Ihl-Vahl R, Marquetant R. Molecular biology of adrenergic receptors. J Hypertens 10:501, 1992
132. Dontenwill M, Tibirica E, Greney H, et al. Role of imidazoline receptors in cardiovascular regulation. Am J Cardiol 74:3A, 1994
133. van Zweiten PA. α-Adrenoceptor-blocking agents in the treatment of hypertension. *In* Laragh JH, Brenner BM (eds): Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York, Raven Press, 1995, pp 2917
134. Sinaiko AR. Influence of adrenergic nervous system on vasodilator-induced renin release in the conscious rat. Proc Soc Exp Biol Med 167:25, 1981
135. Meier J. β-Adrenoceptor-blocking agents. Cardiology 64 (Suppl 1):1, 1979
136. Fitzgerald JD. The applied pharmacology of beta-adrenoceptor agonists (beta-blockers) in relation to clinical outcomes. Cardiovasc Drugs Ther 5:561, 1991
137. Izzo JL Jr, Horwitz D, Keiser HR. Physiologic mechanisms opposing the hemodynamic effects of prazosin. Clin Pharmacol Ther 29:7, 1981
138. Kincaid-Smith PS. Alpha blockade. An overview of efficacy data. Am J Med 82:21, 1987
139. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: Results of a Veterans Administration Cooperative Study. N Engl J Med 314:1547, 1986
140. Opie LH. Role of vasodilation in the antihypertensive and antianginal effects of labetalol: Implications for therapy of combined hypertension and angina. Cardiovasc Drug Ther 2:369, 1988
141. Lin M-S, McNay JL, Shepherd AMM, et al. Increased plasma norepinephrine accompanies persistent tachycardia after hydralazine. Hypertension 5:257, 1983
142. van den Meiracker AH, Man in't Veld AJ, Admiraal PJJ, et al. Partial escape of angiotensin converting enzyme (ACE) inhibition during prolonged ACE inhibitor treatment: Does it exist and does it affect the antihypertensive response? J Hypertens 10:803, 1992
143. Gavras H, Garvas I, Textor S, et al. Effect of angiotensin converting enzyme inhibition on blood pressure, plasma renin activity, and plasma aldosterone in essential hypertension. J Clin Endocrinol Metab 46:220, 1977
144. Quilley J, Duchin KL, Hudes EM, et al. The antihypertensive effect of captopril in essential hypertension: Relationship to prostaglandins and the kallikrein-kinin system. J Hypertens 5:121, 1987
145. Wang D-H, Prewitt RL. Captopril reduces aortic microvascular growth in hypertensive and normotensive rats. Hypertension 15:68, 1990
146. Tolins J, Raij L. Antihypertensive therapy and the progression of chronic renal disease: Are there renoprotective drugs? Semin Nephrol 11:538, 1991
147. Fox PR. The effect of drug therapy on clinical characteristics and outcomes of dogs with heart failure. Scientific Proceedings, 10th Annual Veterinary Medical Forum, Am Coll Vet Int Med, 1992, p 592
148. Fox PR, Sisson DD. Angiotensin-converting enzyme inhibitors: Current uses. *In* Bonagura JD, Kirk RW (eds): Kirk's Current Veterinary Therapy. Vol XII. Philadelphia, WB Saunders, 1995, p 786
149. Longhofer SL, Ericsson GF, Benitz AM, et al. Renal effects of two starting doses of enalapril maleate in dogs with heart failure. J Vet Intern Med 7:124(A), 1993

150. Wysocki M, Persson B, Bagge U, et al. Flow resistance and its components in hypertensive men treated with the calcium antagonist isradipine. Eur J Clin Pharmacol 43:463, 1992
151. Pion PD. Current uses and hazards of calcium channel blocking agents. *In* Kirk RW, Bonagura JD (eds): Kirk's Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1992, p 684
152. Atkins C, Johnson L, Keene B, et al. Diltiazem pharmacokinetics and pharmacodynamics in cats. J Vet Intern Med 8:144, 1994
153. Opie LH. Calcium channel antagonists. Part I: Fundamental properties: Mechanisms, classification, sites of action. Cardiovasc Drugs Ther 1:411, 1987
154. Snyder PS. Evaluation of the antihypertensive agent amlodipine besylate in normotensive cats and cats with systemic hypertension. J Vet Intern Med 8:147, 1994
155. Henik RA, Snyder PS, Volk LM. Amlodipine besylate therapy in cats with systemic arterial hypertension secondary to chronic renal disease. J Vet Intern Med 8:145, 1994
155a. Snyder PS. Blinded clinical trial of amlodipine in cats with hypertension (Abstr). J Vet Int Med 11:139, 1997
156. Calhoun DA, Oparil S. Treatment of hypertensive crisis. N Engl J Med 323:1117, 1990
157. Paulson OB, Strandgaard S. Hypertensive disease and cerebral circulation. *In* Laragh JH, Brenner BM (eds): Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York, Raven Press, 1995, p 465

VII

Cardiovascular Pathology

36

Cardiovascular Pathology

SI-KWANG LIU
PHILIP R. FOX

THE ROLE OF CARDIOVASCULAR PATHOLOGY IN PRACTICE

Clinical interest in veterinary cardiology began in the 1960s, stimulated by information gained from postmortem evaluations. Despite many scientific advances, the goal of reducing cardiovascular morbidity and mortality remains one of the most vexing challenges. Accordingly, interaction between practitioner and pathologist is essential to maximize clinical insight, validate diagnostic and treatment methods, and determine pathologic consequences of heart disease (Table 36–1).[1]

EXAMINATION OF THE HEART AND GREAT VESSELS

A thorough and careful cardiovascular autopsy is well worth the time and effort. Dissection techniques are best guided by clinical information, as necropsy without insightful clinical input reduces useful outcome. Cardiovascular anatomy and methods for examining the heart are described in chapters 2 and 37, respectively. Detection of gross or histologic cardiovascular lesions may suggest but not guarantee related clinical signs. Lesions can be directly associated with functional significance, or they may hold little relationship to clinical signs and prognosis.

HEART FAILURE

Heart failure is not a disease but a clinical syndrome. It is usually associated with severe cardiovascular structural or functional abnormalities, sympathetic and renin-angiotensin-aldosterone system activation (chapters 3, 11), and poor prognosis. Congestive heart failure is said to be present when transcapillary fluid movement exceeds compensatory lymphatic drainage owing to elevated venous pressures, and plasma filtrate accumulates in the lungs as pulmonary edema, or in serosal body cavities as effusions.

CARDIOVASCULAR RESPONSES AND PATHOLOGY IN HEART FAILURE

Cardiovascular pathology may be directly attributable to congenital or acquired diseases causing structural, functional, or inflammatory abnormalities. In addition, lesions may result from altered hemodynamics, neuroendocrine or immune system activation, or metabolic derangements.[2, 3] Extracardiac manifestations of a failing heart are often present.

CARDIAC HYPERTROPHY

One of the major cardiac adjustments to increased demand for cardiac work is compensatory hypertrophy.[3] Two classic forms of left ventricular hypertrophy have been described.[2] In *concentric hypertrophy*, ventricular wall thickening results from adding sarcomeres in parallel without an increase in internal chamber diameter. It is a typical response to pressure overloads such as aortic stenosis or sustained severe arterial hypertension, and it is related to increased ventricular systolic wall tension and increased afterload.[4] *Eccentric hypertrophy* causes a proportional increase in ventricular wall thickness and internal chamber diameter via synthesis of sarcomeres in series. It is common in volume overload and is associated with a number of adverse consequences, including increased diastolic wall tension.[5]

MYOCARDIAL CELL DEATH

Two mechanisms of cell death have been reported. One is accidental cell death through necrosis. The other is programmed death through apoptosis. Each has certain distinguishing features (Table 36–2).[6–10]

Necrosis

Cellular necrosis, a passive process resulting from lethal insult, is characterized by cell membrane rupture and associated inflammation.[6, 7] This is typified by cellular swelling, loss of cell membrane integrity and breakdown, nuclear chromatin clumping into poorly defined masses, swelling and disruption of sarcoplasmic reticulum and mitochondria, formation of granular mitochondrial matrix densities, and loss of calcium and electrolyte homeostasis. These morphologic derangements often play a vital role in the deterioration of cardiac function (Figs. 36–1 through 36–5).

TABLE 36–1
Five Key Cardiovascular Questions to Ask When Seeking to Optimize Clinical Outcome

1. When is the heart anatomically normal?
2. When is the necropsy examination not the gold standard for diagnosis?
3. Are necropsy abnormalities (when present) related to the cause of death and clinical signs during life?
4. Are detectible cardiovascular abnormalities helpful for prognosis?
5. How do autopsy or biopsy findings improve accuracy of noninvasive tests and therapies?

TABLE 36–2
Characteristic Differences: Cell Death Caused by Necrosis and Apoptosis[8]

	Necrosis	*Apoptosis*
Morphologic Differences		
Cell death	Cells die in groups	Deletion of single cells
Cell membrane changes	Loss of integrity	No integrity loss; membrane blebbing
Cell morphology changes	Cellular swelling and lysis	Cells shrink (ultimately form "apoptotic bodies")
Inflammatory response	Yes	No
Phagocytosis	By macrophages	By adjacent normal cells, some macrophages
Lysosomal integrity	Leakage	Intact
Chromatin changes	Clumping and poorly defined aggregation	Compacted into uniformly dense material
Biochemical Characteristics		
Energy	Required	Not required
Process	Loss of ion homeostasis regulation	Tightly regulated process (synthetic and activation steps)
Synthesis requirements	No requirement for protein or nucleic acid synthesis	Requires macromolecular synthesis
Gene transcription	No new transcription	*De novo* transcription
Effects on DNA	Random DNA digestion	Nonrandom oligonucleosomal length DNA fragmentation

From Thompson HJ, Strange R, Schedin PJ. Apoptosis in the genesis and prevention of cancer. Cancer Epidemiol Biomarkers Prev 1:597–602, 1992, with permission.

Apoptosis (Programmed Cell Death)

Apoptosis, also known as "programmed cell death," occurs in the absence of cell membrane rupture and inflammation. It is an active, regulated, energy-requiring process under genetic control,[8–10] characterized by nuclear DNA fragmentation. Nuclear chromatin becomes compacted and segmented into sharply delineated masses along the nuclear margins; the cytoplasm condenses; nuclear fragmentation occurs; the cell surface develops pediculated protuberances and separates

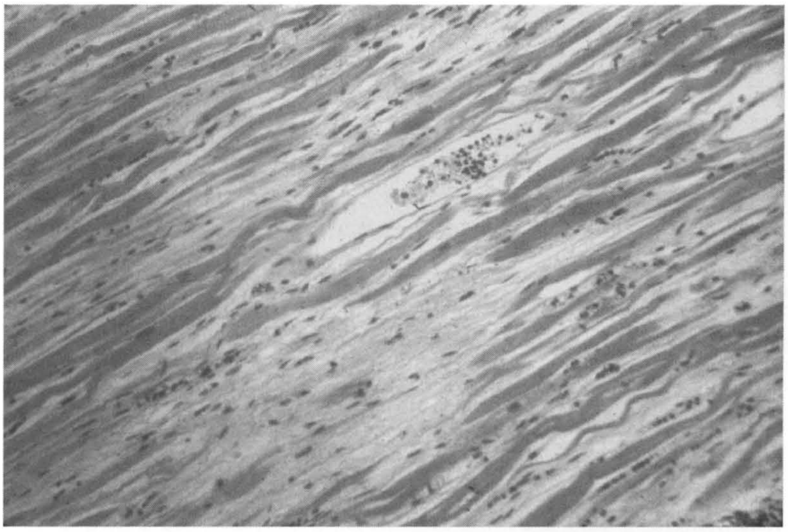


FIGURE 36–1

Histologic section of ventricular septal myocardium from a 4-year-old male Doberman pinscher with dilated cardiomyopathy. Myocytes are elongated, wavy, and attenuated and are surrounded by extracellular ground substance. Substantial areas of myocyte degeneration and myocytolysis are seen. Notice a centrally situated region of extensive myocyte loss with substituted extracellular edematous ground substance. H&E stain × 100.

into membrane-bound "apoptotic bodies" which are phagocytized by adjacent cells. Morphologic and biochemical features of cardiocyte apoptosis have been reported in canine left ventricular myocardium with experimental chronic heart failure,[9] and in humans with end-stage cardiomyopathy.[10] Cardiocyte apoptosis may thus play a role in heart failure.

PATHOLOGIC ALTERATIONS OF MYOCYTE-CONNECTIVE TISSUE

The heart is composed of parenchyma and stroma. Parenchyma consists of cardiac myocytes that are highly differentiated and perform specialized functions. Stroma contains cellular elements, including fibroblasts and macrophages, which, in contrast, are not well differentiated, and whose physiologic behavior and phenotype are affected by circulating and local chemical mediators and signals.[11]

Fibrosis

Fibroblasts have extensive clonal heterogeneity and diversity with regard to morphology, structural protein synthesis, receptor expression, and their response to regulatory molecules.[12] *Fibrosis* represents disproportionate stromal growth with increased myocardial collagen content. Abnormal fibrous tissue can be perivascular, interstitial, or endocardial in location. It can result from tissue irritation, invasion, and other causes and is deemed *reactive fibrosis. Reparative (replacement) fibrosis* represents microscopic scarring in response to myocyte necrosis from any cause (see Fig. 36–2; see also Color Plates 11 and 12). Pathologic myocardial *remodeling* results when either form of fibrosis occurs.[11]

Mechanisms that dictate how and when myocytes have been irreversibly injured, and thus destined for necrosis and potentially reactive or replacement fibrosis, are obscure. In cardiomyopathic cats, widespread focal myocardial cell death and replacement fibrosis

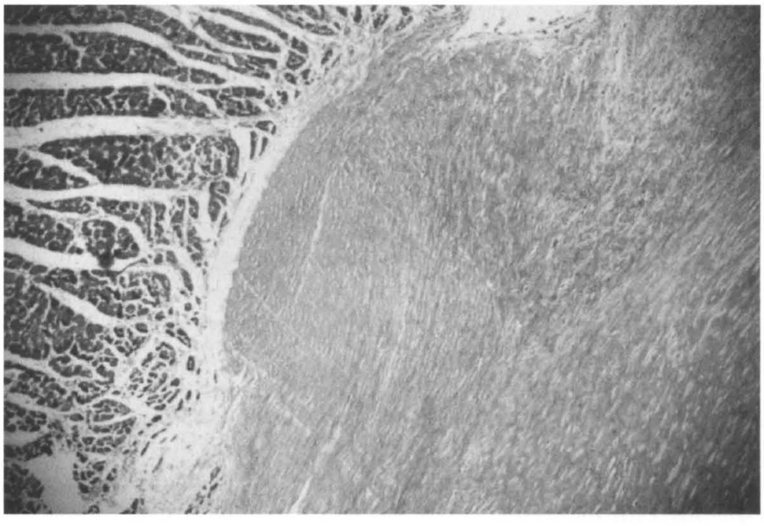


FIGURE 36–2

Histologic section of left ventricular free wall myocardium from a domestic short-hair cat with hypertrophic cardiomyopathy. There is an extensive region of massive replacement fibrosis (lighter appearing tissue relative to darker staining myocytes to the left of this image). Myocyte degeneration is also evident. Masson's trichrome stain × 40.

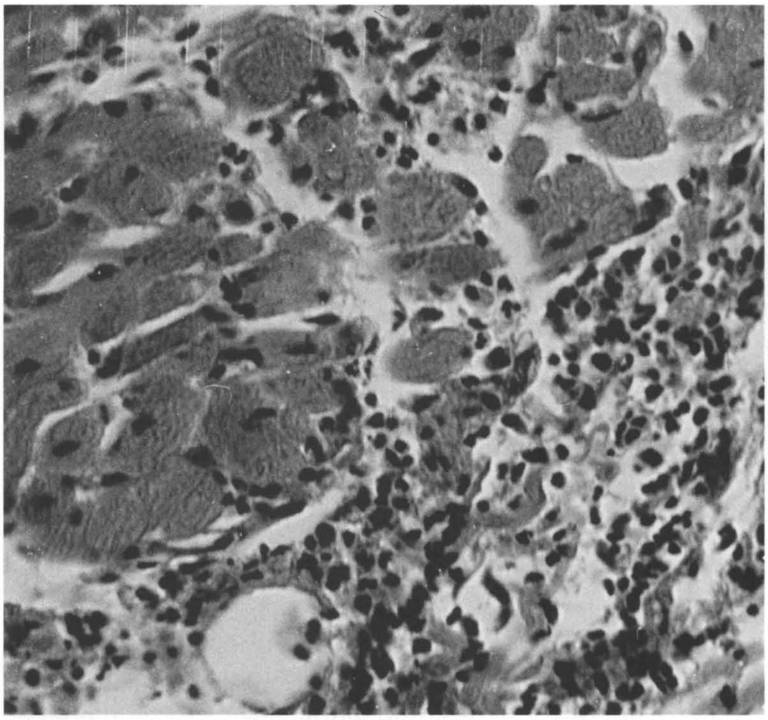


FIGURE 36–3

Histologic section of myocardium from an 18-month-old male, domestic short-hair cat with myocarditis. Notice focal infiltration of lymphocytes, plasma cells, and neutrophils within and adjacent to myocytes. Myocyte degeneration and necrosis are evident, especially toward the bottom right of this photomicrograph. H&E stain × 150.

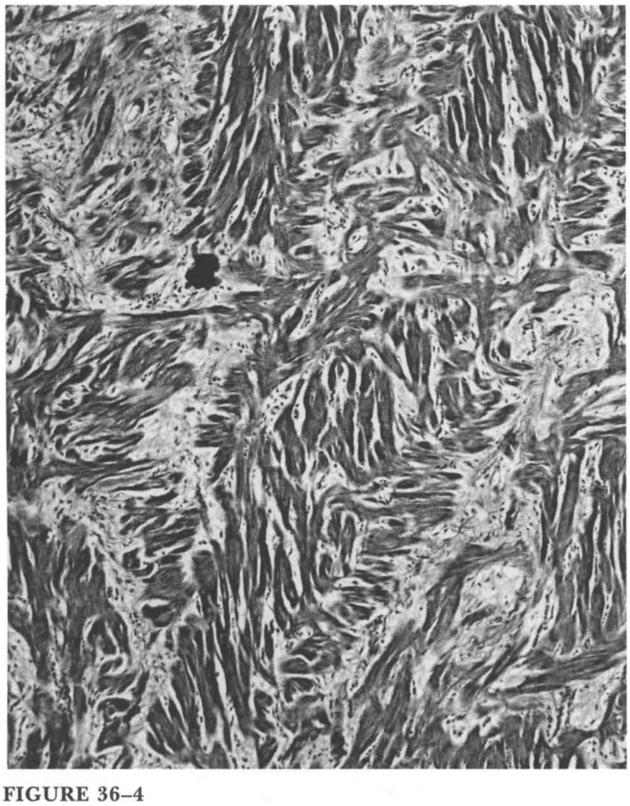


FIGURE 36–4

Histologic section from the ventricular septum of a 6-year-old domestic short-hair cat with hypertrophic cardiomyopathy. Notice the marked myofiber disorganization; instead of the normal parallel myocyte orientation, the myocytes are arranged at oblique or perpendicular angles constituting type I fiber disarray. In addition there is some myocytolysis, and myocytes are separated by severe plexiform fibrosis. H&E stain × 100.

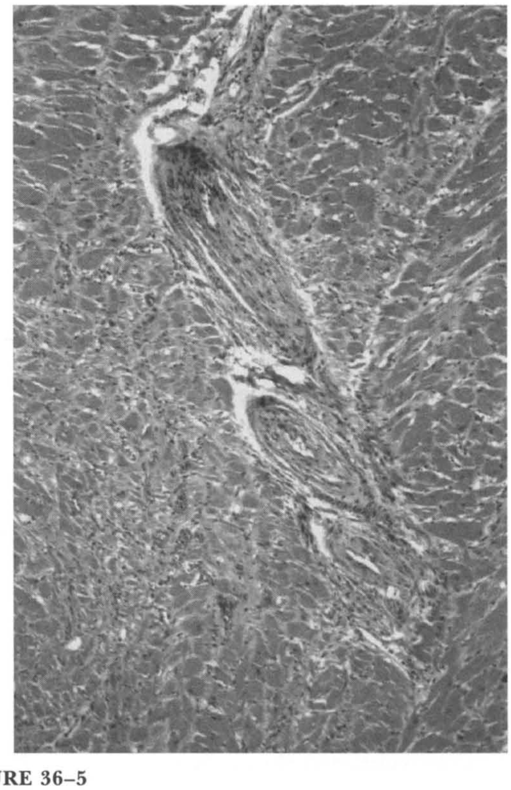


FIGURE 36–5

Histologic section of ventricular septal myocardium from a cat with hypertrophic cardiomyopathy. Three abnormal intramural coronary arteries are evident. They exhibit severe luminal narrowing due to smooth muscle proliferation and increased connective tissue elements ("small vessel disease"). There is also mild to moderate intermyocyte fibrosis and diffuse myocytolysis, which is predominant adjacent to regions of fibrosis. H&E stain × 100.

occur, which influences myocardial dysfunction, morbidity, and mortality. As has been described in hypertrophic cardiomyopathy, cardiomyocyte cell death and fibrosis is frequently located proximal to abnormal intramural coronary arteries, suggesting an association.[13, 14]

Morphologic studies of fibrous tissue responses in experimental models of arterial hypertension suggest a causal relationship between progressive structural myocardial remodeling that includes perivascular fibrosis extending into the interstitial space, and activation of the renin-angiotensin-aldosterone system.[15, 16] The activities of fibroblast-like cells (*myofibroblasts*) to regulate collagen turnover are the subject of much investigation. These cells elaborate type III and then type I collagen, which is the major fibrillar collagen in fibrous tissue.[17, 18]

Interstitial Matrix Changes

Myocytes are enmeshed in an elaborate stromal framework containing collagen, elastin, and other elements.[19] The interstitial matrix, of which collagen is the major component, represents networks of pericellular, interstitial, and fascicular connective tissue. Myocardial cells are diffusely interconnected by this connective tissue framework, which is composed of struts, pericellular weaves, and coiled perimysial fibers. This internal myocardial skeletal framework is thought to participate in myocardial function, integrate individual myocytes into three-dimensional conformational changes during systole, and contribute to myocardial compliance during diastole. When altered in cardiac disease, abnormal matrix architecture may contribute to cardiac dysfunction.[20, 21] Unlike pathologic fibrosis, which can be identified by standard hematoxylin and eosin or Masson's trichrome stain, matrix components can only be visualized histologically by specialized staining techniques (Fig. 36–6).

FIGURE 36–6

Histologic section of ventricular septal myocardium from a domestic short-hair cat with restrictive cardiomyopathy. The morphology of interstitial collagen connective tissue is markedly altered and includes increased bundles of perimysial coils and accentuated fibrous weaves. Modified Hortega silver stain × 150.

PULMONARY EDEMA

Left-sided heart failure results in pulmonary edema. Edematous lungs are wet and heavy, may not float, do not collapse completely when the thorax is opened, and ooze edema fluid from cut sections. Interstitial edema may be clear or slightly yellow. Hemorrhage causes a pinkish staining of fluid or foam. Microscopically, edema fluid is acidophilic or faintly granular, filling alveoli, interstitium, and lymphatics. Protein content is very low. Capillaries and lymphatics are distended. Intra-alveolar hemorrhage is evident. Alveolar macrophages ("heart failure" cells) containing erythrocytes or hemosiderin are present and increase with the duration of edema. Chronic cardiogenic edema and associated pulmonary hypertension may cause muscular hypertrophy of small pulmonary arteries and fibrous thickening of pulmonary capillary walls. Occasionally, in fulminant, terminal pulmonary edema, leukocytes accumulate in pulmonary capillaries, endothelial damage and alveolar type I epithelial cells are noted, and fibrin-rich fluid fills the alveoli.[22]

EFFUSIONS

Right-sided heart failure is characterized by abdominal, pleural, and/or pericardial effusions, which are generally sterile, obstructive transudates. Smears contain a mixture of blood cells and lymphocytes, with a nucleated cell–to–red cell ratio roughly equal to that of blood, and some mesothelial cells. With time, the effusion becomes modified and acquires greater numbers of inflammatory cells and increased protein. In long-standing effusions, mesothelial cells and macrophages may exhibit erythrophagia.[23, 24] Occasionally, chylous effusion may occur; it appears milky white, with mostly lymphocytes and variable numbers of neutrophils, depending on the duration and degree of pleuritis.[25] With long-standing pleural effusions of modified transudate or chyle, pleuritis may cause lung lobe borders to become fibrotic or even collapse. Chronic ascites or pericardial effusion may result in fibrin deposition, especially evident around the liver

in the former, and adherent to epicardial surfaces in the latter.

HEPATIC CONGESTION

Passive hepatic congestion accompanying chronic right-sided heart failure causes time-related pathologic changes.[26] Acute passive congestion results in a swollen liver that appears dark and bloody when sectioned. Little accentuation of the acinar pattern is evident. Extruded hepatic lymph is rich in clotting factors and may cause large fibrin deposits on the capsule or between lobes. Microscopically, there is uniform sinusoidal engorgement, with rapidly following fatty change, atrophy, and necrosis of periacinar hepatocytes. More chronic passive congestion causes the capsule to assume a finely nodular texture. Edges of the central lobes become rounded. A reticulated acinar pattern is evident in sliced sections. This "nutmeg" appearance is caused by the contrast of red-colored periacinar necrosis and blood replacement with pale, slightly raised periportal tissue composed of fatty hepatocytes. Histologically, fibrous tissue infiltrates the stroma and periacinar zones, outlining simple and compound acini ("cardiac fibrosis").

CLINICAL PATHOLOGY

A variety of laboratory tests may be useful in diagnosing cardiovascular abnormalities, assessing the effects of drugs or cardiovascular disease on other organ systems, and revealing systemic and metabolic disorders causing or precipitating heart failure (chapter 33). Anemia and thyrotoxicosis may result in high-output heart failure (chapter 34). Hyperthyroidism and chronic renal failure may cause arterial hypertension (chapter 35). Elevations of serum creatine kinase, lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase may accompany coagulopathies associated with systemic thromboembolism (chapter 28). Heartworm testing, cytologic evaluation of effusions, biochemical profiles, and other tests provide useful information in selected cases.

CONGENITAL CARDIOVASCULAR DISORDERS

Congenital cardiovascular malformations are often dynamic anomalies that originate in fetal life (chapter 1) and change during postnatal development (chapter 24).[27] They represent structural abnormalities of the heart, valves, or great vessels and constitute a small but clinically important cause of cardiovascular disease in dogs and cats (chapters 23, 24).[28] In canines, the incidence has been reported as 6.8 (0.68%) per 1000 dogs at the University of Pennsylvania during 1987 to 1989, and 8.5 per 1000 dogs from the nationwide Veterinary Medical Data Base during the same interval.[29] In felines, a necropsy incidence of 28 per 1000 autopsies (2.8%) was reported at Angell Memorial Hospital[30] and 19 per 1000 necropsies at the Animal Medical Center.[31] Inherited arrhythmias are rare, but ventricular arrhythmias and sudden death have been reported in German shepherd dogs.[32]

VENTRICULAR OUTFLOW OBSTRUCTIONS

AORTIC STENOSIS

Congenital fixed obstruction to left ventricular outflow can be valvular, subvalvular, or supravalvular and may be accompanied by other defects. In dogs, the stenosis is usually subvalvular and represents one of the most important canine developmental anomalies;[28, 33] isolated valvular and supravalvular stenosis are rare. Subaortic stenosis (SAS) is generally caused by a subvalvular fibrous ring obstructing the LV outflow tract (see Figs. 8–19; 24–12, 24–19). A mode of inheritance has been reported in Newfoundland dogs as polygenic or autosomal-dominant (with modifiers). This subvalvular obstruction may not necessarily be present at birth and may develop within the first 4 to 8 weeks.[34]

In cats, subvalvular (see Fig. 24–22*A*) and supravalvular forms of congenital aortic stenosis have been rarely described;[30, 31, 35, 36] some cases may be confused with variants of hypertrophic cardiomyopathy.

GROSS FINDINGS. Several morphologic types of canine SAS have been described from necropsy: (1) *grade 1* indicates the mildest form, in which small, slightly raised nodules are present on the endocardial surface of the interventricular septum immediately below the aortic valve; (2) *grade 2* indicates a narrow fibrous ridge extending partially around the LV outflow tract; (3) *grade 3* represents the most severe form, in which a subaortic fibrous band, ridge, or collar completely encircles the LV outflow tract.[34, 37] In the most severe cases, a fibromuscular collar can insert onto the anterior mitral valve leaflet. Aortic valve leaflets may be thickened. The pressure overload of moderate to severe SAS causes LV pressure overload and associated concentric LV hypertrophy; left atrial hypertrophy results from the elevated pressures required to fill the thick, stiff left ventricle; poststenotic dilatation of the ascending aorta occurs with moderate to severe SAS (see Figs. 24–15, 24–22). Jet lesions may be present. Bacterial endocarditis involving the aortic valves may result from valvular endothelial injury. A less common

form of fixed obstruction to LV outflow is a "tunnel" or "tubular" aortic stenosis in which a fibromuscular channel occupies a portion of the LV outflow tract.

In felines, aortic valve leaflets are usually malformed regardless of the stenotic location. Affected cats are often stunted, and acute heart failure has been reported to develop before 18 months of age.[31]

HISTOLOGIC FEATURES. The stenotic ring consists of collagen, loosely arranged reticular fibers, elastic fibers, ground substance, and, occasionally, cartilage in severe lesions.[34] Severe fibrous lesions may encroach upon or affect the aortic valve cusps, which may themselves be somewhat fibrotic. In cases of moderate to severe aortic stenosis, myocardial fibrosis may be present (see Fig. 24–13). Intramural coronary artery abnormalities may be detected, including connective tissue and smooth muscle proliferation and degeneration of the vascular media.[38, 39]

PULMONIC STENOSIS

Pulmonic stenosis (PS) is a common canine congenital heart defect,[28, 40–42] but it is rarely detected as an isolated lesion in the cat.[31, 43–46] Obstruction to right ventricular ejection may occur at the infundibular, subvalvular, valvular, or supravalvular locations. In dogs, pulmonary valve dysplasia is the most common form of PS (see Figs. 24–2, 24–3, Color Plate 3). Pulmonic stenosis has a hereditary basis in certain canine breeds and has been shown to have a polygenic mode of transmission in beagles.[42] It may be accompanied by other defects, especially tricuspid dysplasia. In cats, isolated lesions are rare, but dysplasia of the pulmonic valve and infundibular hypertrophy have been reported.[43–46] Valvular or subvalvular PS or both are components of tetralogy of Fallot. Pulmonary artery atresia represents the extreme variant of PS. Dogs may be asymptomatic or develop low cardiac output with syncope or lethargy, or right-sided heart failure. Felines are usually stunted, display intermittent dyspnea and cyanosis, and ultimately die within the first year of life.[43, 44]

GROSS FINDINGS. In beagles with pulmonary valve stenosis, gross abnormalities comprised a spectrum of lesions graded as follows:[42] grade 1 — slight thickening of pulmonary valve leaflets with little or no fusion or hypoplasia, resulting in little or no outflow tract gradient; grade 2 — moderate to severe thickening of pulmonary valve leaflets with fusion and/or hypoplasia resulting in moderate to severe outflow obstruction. Other forms of PS are characterized by stricture of the main pulmonary artery above the valve (supraventricular PS) or narrowing of the right ventricular outflow tract proximal to the pulmonic valve (subvalvular PS). Some dogs with valvular PS have fibrous thickening immediately below the valves. The pulmonic valve annulus may be hypoplastic (see Fig. 24–2). Moderate to severe PS causes poststenotic dilatation of the main pulmonary artery (see Figs. 8–20*A*; 24–8, 24–10); RV pressure overload with associated right ventricular hypertrophy (see Figs. 8–20*B*; 24–9); and tricuspid insufficiency with RA enlargement (see Fig. 24–5).[47] Anomalous coronary artery development may occur in some dogs, particularly brachycephalic breeds (see Fig. 24–3), in which a single coronary artery encircles the stenotic RV outflow outlet and valve.[48]

HISTOLOGIC FEATURES. Valvular changes include thickening of the pulmonary valve spongiosa with loosely arranged connective tissue; bands of fusiform cells in a dense collagen network; and blood-filled, endothelium-lined spaces. The fibroelastic band of the reticularis layer may be fragmented, reduced, or absent.[40, 42]

OBSTRUCTION TO ATRIAL INFLOW: MITRAL AND TRICUSPID STENOSIS AND COR TRIATRIATUM

Although these disorders have been reported infrequently, the increasing use of echocardiography should increase antemortem diagnosis. Physiologic consequences are related to elevated venous filling pressures and secondary venous hypertension.

MITRAL AND TRICUSPID STENOSIS

Congenital mitral stenosis (MS) or tricuspid stenosis (TS) may involve the atrioventricular valve apparatus (i.e., annulus, valve leaflets, chordae tendineae, and papillary muscles), or occur immediately above or contiguous with the annulus (see Figs. 24–54, 24–56).[27, 49–51] In dogs, mitral stenosis may be more common in breeds that are prone to congenital mitral valve malformations, such as the bull terrier and Newfoundland, and may be associated with other cardiac malformations.[49, 50] In cats, reports of MS are limited but suggest that the lesion may be associated with mitral valve complex malformation or, less commonly, a supravalvular membrane.[51] Left atrial enlargement (see Fig. 24–59) results principally from obstruction of transmitral flow and secondarily from mitral regurgitation. Left-sided CHF was observed in 11 of 15 affected dogs within 1 year of diagnosis in one study,[50] and in all 3 cats from another report.[51] Infrequently, MS may result from intracardiac tumors or vegetative endocarditis in dogs, or from left atrial ball thrombi in cats.

Tricuspid stenosis is rare.[28, 31, 52, 53] Some cases may represent severe states of tricuspid valve dysplasia for which Labrador retrievers appear to be at increased risk.[29] Severe TS may cause pronounced RA enlargement and right-sided heart failure.

COR TRIATRIATUM

This rare lesion is caused by partition of either atrium by an intra-atrial membrane of disputed embryogenesis, resulting in two compartments joined by an opening or openings. The size of these openings determines the degree of obstruction. *Cor triatriatum dexter* (see Fig. 24–60) is caused by an anomalous septum located within the right atrium or at the junction of the caudal vena cava and right atrium.[54–57] This usually results in clinical manifestations of a Budd-Chiari–like syndrome (postsinusoidal portal hypertension with hepatomegaly and ascites). *Cor triatriatum sinister* results from an LA partition.[58] Pulmonary edema may develop.

ATRIOVENTRICULAR VALVE DYSPLASIA AND INSUFFICIENCY

Malformations of the AV valves are prevalent in cats, in which they constitute the most common congenital disorder.[45–17] In dogs, they are reported less frequently but predominantly in large breeds. Abnormalities comprise a broad spectrum of structural and functional derangements in either the mitral or tricuspid valve complex—i.e., the annulus, AV valve leaflets, chordae tendineae, papillary muscles, and associated myocardium. Generally, malformation causes atrioventricular valve incompetence, but it may occasionally result in stenosis. Other congenital heart anomalies may be present in affected animals, and malformations of both AV valves often occur concomitantly.

GROSS FINDINGS. Atrioventricular valve complex alterations (see Figs. 24–54 to 24–56) may include enlarged annulus; valve leaflet shortening with thickening, rolled edges, or fused commissures; chordae tendineae that are shortened and thickened (occasionally lengthened), with abnormal valve leaflet attachments and alignments (sometimes horizontally attached to leaflets); upward malposition of atrophic or hypertrophic papillary muscles; or insertion of one papillary muscle directly into one or both valve leaflets. With tricuspid valve dysplasia, there may be adherence or direct insertion of the septal leaflet onto the right ventricular wall. Severe valve dysplasia may result in greater than normal heart weights, eccentric dilation of the affected ventricle, and marked atrial enlargement and hypertrophy. Congestive heart failure occurs in severe cases due to volume overload.

HISTOLOGIC FEATURES. There is proliferation of spongiosa, hypoelastification, and irregular arrangement of fibrosa in affected leaflets. Endothelium-lined, blood-filled cysts may occur in valve tissue.

CONGENITAL DEFECTS CAUSING SYSTEMIC-TO-PULMONARY (LEFT-TO-RIGHT) SHUNTING

PATENT DUCTUS ARTERIOSUS

Normally the ductus arteriosus closes during the first few days of life. If it remains patent, it causes left-to-right shunting of blood from the aorta to pulmonary artery and lungs and, thus, increased venous return to the left heart (see Figs. 1–5; 24–40). Patent ductus arteriosus (PDA) is the most commonly reported canine congenital heart anomaly[28, 59–67] and is well recognized in the cat.[68–70] An inherited mode of transmission has been described in canines.[59]

GROSS FINDINGS. The PDA opens into the main pulmonary trunk just proximal to the pulmonary artery bifurcation (see Figs. 8–16; 24–22*A*, 24–39). In left-to-right shunting PDA, increased volume overload causes left ventricular dilation and hypertrophy; left atrial dilation; enlargement of the aortic arch (descending aorta) at the level of the PDA; and enlargement of the main pulmonary artery. The main pulmonary artery may be dilated and display intimal fibrosis (i.e., *jet lesions*) near the ductus. Congestive heart failure (usually left-sided, occasionally biventricular) occurs in most animals if the PDA remains uncorrected. A nonpatent *forme fruste diverticulum* may occur in which the ductus is completely closed at one end (usually at the pulmonary artery junction), causing an aortic ductus diverticulum.[28, 61, 62, 65, 71] At least four clinical types of PDA with varying patency have been described: type I (small PDA), no aneurysm; type II (medium-sized), small to medium-sized aneurysm; type 3a (large PDA before CHF), marked left-sided heart enlargement and medium to large ductus; type 3b (large PDA plus CHF), other conditions similar to 3a; and type 4 (large PDA plus pulmonary hypertension [cyanotic heart disease]), large RA, RV, and main pulmonary artery.[71] Occasionally, an aorticopulmonary septal defect (i.e., "window") occurs between the ascending aorta and pulmonary trunk rather than a patent ductus arteriosus.[72]

If pulmonary hypertension develops, RV hypertrophy may occur (see Fig. 24–41*B*, *C*). In right-to-left shunting PDA, a large-diameter ductus may be present with pulmonary arterial medial hyperplasia, RV hypertrophy, and hypoplasia of the LV, LA, and ascending aorta.

HISTOLOGIC FEATURES. In the dog, failure of the ductus to close results from lack of normal or asymmetric distribution of ductus-specific, circumferential smooth muscle in the fetal ductal wall and a reciprocal increase in elastic tissue in areas that should be muscular.[73] These abnormalities preclude normal ductal sphincter

closure in response to increased oxygen tension after birth.

ATRIAL SEPTAL DEFECTS

Atrial septal defects (ASDs) represent a through-and-through communication between the atria.[28, 74–81] Although shunting depends upon the caliber of the orifice and the relative degree of systemic and pulmonary circulatory resistance, blood usually shunts from the left to the right atrium (see Fig. 24–27; Color Plates 7–9). Isolated ASDs are rare in dogs and cats;[28, 30, 74, 77–81] they comprise an important component of the endocardial cushion defect occurring most often in felines.[75, 76] ASDs are often present with other congenital heart anomalies (see Fig. 24–26). Large defects with left-to-right shunts are uncommon, but when present, may cause a volume overload and associated enlargement of the RA, RV, and main pulmonary artery.

GROSS FINDINGS. Classification of ASDs is based upon the anatomic region of the malformation (see Fig. 1–3).[27] *Ostium primum* defects lie in the lower atrial septum (see Figs. 24–25; 24–26*B*). They are uncommon as isolated lesions and are more significant when they form part of a common AV canal *(endocardial cushion defect). Ostium secundum* defects are the most common type; these involve the region of the fossa ovalis forming in the middle portion of the interatrial septum (see Figs. 8–2; 24–25). Ostium secundum defects may result from a shortened valve of the foramen ovale, excessive or ectopic resorption of the septum primum, or a deficiency of septal growth. *Sinus venosus* ASD is a rare variant of ostium secundum ASD, occurring high in the atrial septum at the junction of the cranial vena cava (see Fig. 8–3).[81] A patent foramen ovale (see Fig. 24–26*A*) is not a true ASD since atrial septa are present. It may be detected with conditions that increase right atrial pressure (tricuspid insufficiency or tricuspid stenosis, or severe pulmonic stenosis). Its flaplike valve permits blood flow only from the right to left atrium.

ATRIOVENTRICULAR SEPTAL DEFECTS (ENDOCARDIAL CUSHION DEFECT)

Patency of the atrioventricular septum has traditionally been known as an *endocardial cushion defect.* This was based upon the assumption that endocardial cushion tissue contributes significantly to formation of adjacent atrial and ventricular septal structures and contiguous AV valve leaflets (see Fig. 1–3).[82] As this morphogenesis has been called into question, the term *atrioventricular septal defect* has come to designate a group of lesions in which the atrioventricular septum is absent.[83] This malformation is relatively common in the cat. Complete endocardial cushion defects have been termed *common AV canal,* as all four cardiac chambers communicate. Affected animals usually develop severe, generalized cardiomegaly, are stunted, and die of CHF before 1 year of age.[28, 30, 74–76]

GROSS FINDINGS. Predominant features include absence of atrioventricular septum; a common atrioventricular orifice with a common fibrous ring—or separate right and left AV valvular components; and malformation of AV valves, including cleft anterior mitral leaflet or common atrioventricular valve that guards the orifice. The common AV orifice lies along the same horizontal plane, whereas normal AV valves have two separate orifices that lie in different planes.

VENTRICULAR SEPTAL DEFECTS

Ventricular septal defects (VSDs) are relatively common in cats and perhaps occur less frequently in dogs.[27, 30, 74, 84, 85] Most are left-to-right shunting, *restrictive* VSDs, since the defect is usually small and systemic pressures exceed right heart pressures (see Fig. 24–35; Color Plates 8, 9). They may also be components of other malformations (tetralogy of Fallot, endocardial cushion defect) and frequently appear with other disorders such as AV malformations in cats.

GROSS FINDINGS. Most isolated, restrictive VSDs are located high in the membranous portion of the interventricular inlet septum, just beneath the septal tricuspid valve leaflet (see Figs. 8–17*A*; 24–31, 24–32). As viewed from the left ventricular outflow tract, they appear just beneath the aortic valve. When viewed from the right ventricle, they are often described relative to the crista supraventricularis of the ventricular inlet or outlet. They may be partially occluded by the tricuspid leaflet. Prolapse of an aortic valve cusp into the defect may occur (see Fig. 24–33). Rarely, VSDs may occur at other sites throughout the septum (see Fig. 8–17*B*). In large, *nonrestrictive* VSDs in which pulmonary vascular resistance is normal, substantial left-to-right shunting develops; much of the shunt volume is pumped through the VSD into the pulmonary artery, to the lungs, and then returned to the LA, imposing a large volume overload to the left heart. Left atrial and ventricular enlargement and pulmonary edema may develop. If ventricular pressures equilibrate, right ventricular hypertrophy results.

PULMONARY-TO-SYSTEMIC (RIGHT-TO-LEFT) SHUNTING HEART DISEASES

Sometimes termed *cyanotic heart disease,* various lesions result in pulmonary-to-systemic shunting and ar-

terial denaturation. This may occur when defects occur between pulmonary and systemic circulations, coupled with increased pulmonary afterload. The latter may result from obstruction to right ventricular blood flow, such as pulmonary stenosis or increased pulmonary vascular resistance. In this fashion, right-to-left shunting may occur with PDA, aorticopulmonary window, VSD, and ASD.[27] Right ventricular hypertrophy results from increased resistance to RV outflow.

PULMONARY LESIONS WITH EISENMENGER'S PHYSIOLOGY

Eisenmenger's physiology is a state of right-to-left (i.e, "reversed") shunting associated with irreversible pulmonary vascular resistance and pulmonary hypertension.[86–88] Pulmonary arterial lesions (*plexogenic pulmonary arteriopathy*) include intimal thickening and medial hypertrophy of muscular pulmonary arteries and, especially, plexiform lesions.

TETRALOGY OF FALLOT

A widely recognized condition in dogs and cats resulting in right-to-left shunting is tetralogy of Fallot.[27, 30, 31, 89–95] In some canine breeds (keeshond), it is inherited, transmitted as a polygenic trait, and attributable to maldevelopment of the conotruncal system.[89–91] Affected animals often display stunted growth. Sudden death can occur.

GROSS FINDINGS. This anomaly is characterized by four major components (see Figs. 24–47 to 24–50): (1) subaortic ventricular septal defect, (2) biventricular origin (i.e., dextroposition) of the aorta, (3) obstructed right ventricular outflow (pulmonary stenosis), and (4) secondary right ventricular hypertrophy. There is generally mild poststenotic dilatation of the main pulmonary artery, a relatively small left ventricle, and a somewhat widened ascending aorta. In cats, the principal cause of right ventricular outflow tract obstruction is marked hypertrophy of the crista supraventricularis,[31, 46] whereas valvular pulmonary stenosis is the cause of pulmonic stenosis in dogs with tetralogy of Fallot. The term *pseudotruncus arteriosus* describes conditions in which pulmonary atresia is present.

VASCULAR ANOMALIES

A variety of vascular malformations occur in the dog and cat. Patent ductus arteriosus is the most common and clinically important anomaly.[27–31, 59–73] Aortic and thoracic venous anomalies have been described.[95–110] Peripheral vascular disorders,[111, 112] including those of abnormal abdominal venous drainage (portosystemic shunts),[113, 114] are reported. Coronary artery anomalies are most important when associated with congenital pulmonic stenosis (see Fig. 24–3),[48] although various abnormalities have been described.

VASCULAR RING ANOMALIES

Reported mostly in dogs, these malformations are uncommon in cats. Regurgitation results when esophageal obstruction is caused by persistent right aortic arch (the most common ring abnormality)(see Fig. 24–61),[96–102] double aortic arch,[96, 98, 99, 101–103] left aortic arch with ligamentum arteriosum,[98, 104] or retroesophageal subclavian arteries.[96, 98, 99] Figure 1–4 reviews development of the aortic arch system.

AORTIC INTERRUPTION

Malformations of the aorta result in interruption (coarctation)[105] or focal narrowing.[106] These are rare and have been reported only in the dog.

AORTICOPULMONARY SEPTAL DEFECT

Failure of the truncus arteriosus to differentiate causes persistence of aorticopulmonary communication between the ascending aorta and main pulmonary artery.[107, 108] Most cases develop pulmonary hypertension and subsequent right-to-left shunting.[27]

VENOUS ANOMALIES

Persistence of the left cranial vena cava (see Fig. 24–62) is a relatively common venous anomaly that can be complete or incomplete. Aside from reducing exposure during some surgical thoracic procedures or complicating cardiac catheterization, it has no clinical significance and may accompany other congenital disorders.[95, 98, 99, 109] Anomalous pulmonary venous return is rare but is reported in the dog[110] and cat.[30]

PERIPHERAL VASCULAR DISEASES

Peripheral vessels, including arteries, veins, and lymphatics, may become affected secondary to systemic and metabolic diseases or may represent primary vascular disorders.[111, 112] Diseases of arteries include occlusive disorders such as thromboembolism, vasculitis, and arteriopathies, and nonocclusive conditions including arteriovenous fistulas, arteriosclerosis, and atherosclerosis. Venous diseases are uncommon other than phlebitis. Lymphatic disorders occur infrequently, including lymphangitis, lymphedema, and lymphangiectasia. Peripheral vascular neoplasia such as angioma, hemangioma, hematoma, and hemangiosarcoma are well described.

NEONATAL HEART FAILURE ASSOCIATED WITH ATRIOVENTRICULAR VALVULAR MALFORMATION AND ENDOCARDIAL FIBROELASTOSIS

This ubiquitous disorder of uncertain etiology has been variably described as neonatal endocardial fibroelastosis,[115] endocardial fibrosis with cardiomegaly, and possibly, kitten mortality complex.[116] Acute congestive cardiomyopathy with muscle fiber degeneration and associated endocardial fibroelastosis has been reported as a postulated cause of kitten mortality complex.[116]

We have recognized a condition resulting in neonatal death as cardiac failure associated with congenital AV valvular malformation and secondary endocardial fibroplasia. In a series of 26 affected kittens from 16 litters necropsied at the Animal Medical Center, the mean age was 32 days (range, 2 to 70 days). Breeds included domestic short-hair, Siamese, Abyssinian, and Burmese. Litter size was usually small (two or three kittens). Most kittens died suddenly and were depressed, anorectic, and dyspneic for only a few hours before death.

Cats in the Animal Medical Center series displayed many of the pathologic features that were described in humans[117] and cats with endocardial fibroelastosis.[118] Since similar lesions have been reported in association with volume overload with mitral regurgitation,[119] congenital valvular malformations,[31, 120] and following mitral valve replacement in humans,[121] a relationship with volume overload must be suspected. Alternatively, given the relatively high number of feline viral diseases, prenatal viral myocarditis or associated immune-mediated reaction might presumably cause or contribute to this condition. This hypothesis is supported by evidence that human endomyocardial fibroelastosis is a sequela of viral myocarditis with rapid progression to end-stage[121a] (see also chapter 28). Endocardial fibroelastosis has also been reported in the Burmese breed as an inherited anomaly.[118]

GROSS FINDINGS. The heart is often globular in shape, and both atria are enlarged and hypertrophied. Ventricular dilation is evident, and papillary muscles are often upwardly malpositioned. There are pronounced mitral valve malformation, tricuspid valve dysplasia, and widespread opaque areas representing endocardial fibroelastic tissue. The left ventricular free wall tends to be thinner than normal in older kittens. Pulmonary edema, pleural effusion, or ascites may be present.

HISTOLOGIC FEATURES. Myocytes are thin and may display sarcoplasmic coagulation, granulation, vacuolation, fragmentation, and myocytolysis (often severe). They are separated by extracellular edematous ground substance. In very young kittens (generally less than 2 weeks of age), degenerated cellular debris and edematous exudate are observed in the endocardium as well as in and around moderator bands. In kittens aged 3 to 6 weeks, myocytes may be thin and elongated, separated by delicate fibers and extracellular edematous ground substance. Endocardium is thickened by fibroplasia, elastosis, proliferation of myofibrocytes, and Anichkov's cells. In older kittens (generally over 7 weeks), extensive endocardial fibroplasia and elastosis may be noted. Pulmonary alveolar septa are thickened by proliferation of epithelial cells and histiocytes. The alveolar lumens are filled with proteinaceous fluid and active macrophages.

EXCESSIVE LEFT VENTRICULAR MODERATOR BANDS

Heart failure and death have been reported in cats with myocardial disease, characterized by excessive numbers and abnormal complexes of left ventricular moderator bands.[122] Since excessive LV moderator bands have been observed in cats dying of congestive heart failure at 1 week of age, a congenital origin is suspected. Their contribution to cardiomyopathies or congestive heart failure has not been clearly established, however, and in many instances, they have been observed at necropsy as an incidental finding. The variability in number, pattern, density, and severity of abnormal moderator band networks suggests that various phenotypic expressions occur in felines.

GROSS FINDINGS. Affected hearts are small, with irregularly shaped contours, rounded apexes, and occasionally, indentation of the mid left ventricular epicardial surface. Heart weight is significantly lower than for hypertrophic, dilated, or restrictive cardiomyopathic hearts but not significantly less than that of clinically normal hearts. The LV cavity may be irregularly narrowed in some affected hearts. This results when excessive abnormal moderator band networks connect papillary muscles, LV free wall, or both to the ventricular septum (see Fig. 28–25). Pulmonary edema and/or pleural effusion and thromboembolism have been detected in some cats.[122]

HISTOLOGIC FEATURES. The moderator bands consist of central Purkinje's fibers and dense, parallel collagenous fibers covered by endothelium. There is loose, fibrous connective tissue between the endothelium and the collagenous fibers. Some moderator bands are composed of Purkinje's fibers surrounded by loose fibrous connective tissue, adipose tissue, lymphocytes, and blood vessels and covered by endothelium.

ACQUIRED CARDIAC DISEASES

There are numerous acquired cardiovascular disorders. Some are idiopathic and relatively species-specific, such as feline hypertrophic cardiomyopathy or canine myxomatous valvular degeneration (endocardiosis). Many conditions occur secondary to systemic or metabolic disorders (see Chapter 33).

VALVULAR DISEASES

CHRONIC ACQUIRED ATRIOVENTRICULAR VALVULAR DISEASE (MYXOMATOUS DEGENERATION OR ENDOCARDIOSIS)

Chronic acquired valvular disease is a degenerative disorder of predominantly middle-aged and geriatric dogs (chapter 25).[99, 123–129] It has also been termed *endocardiosis*, and *myxomatous transformation* or *degeneration of the AV valves.* In severe cases, significant valvular incompetency, volume overload, and heart failure may result. The atrioventricular valves are most severely affected (Color Plate 10), whereas the pulmonic and aortic valves are less commonly involved. Reported incidence varies from 8.3 percent in one clinical study of 4831 dogs[60] to 64 percent of 550 necropsied dogs.[126] Prevalence and severity increase with advancing age. Although virtually all breeds are affected, it occurs much more frequently in small and toy breeds, in which it represents the most common cause of heart disease.

This abnormality has been infrequently observed in cats. However, it is rarely severe enough to cause significant valvular regurgitation and is usually found in conjunction with myocardial diseases.

GROSS FINDINGS. The mitral valve is abnormal in approximately two thirds of affected dogs; both mitral and tricuspid valves together are abnormal in about one third of cases. Infrequently, the tricuspid valve alone is affected.

Lesions vary widely in severity. Gross anatomic changes (see Figs. 8–21; 25–1) have been described as follows:[125, 125a] type I lesions—earliest changes consist of a few small, discrete nodules or areas of opacity at the points of valve apposition; type II lesions—nodules are larger and more numerous and begin to coalesce; type III lesions—large nodules or plaquelike deformities are present with thickening of chordae tendineae at their valvular attachment sites; type IV lesions—valve cusps are grossly distorted, contracted, rolled upward, and "shrunken," whereas chordae tendineae are usually thickened proximally and are occasionally ruptured. Chordae tendineae may be short and stout or long and thin. Occasionally, AV valve leaflets may be exuberant and balloon or billow into the left atrium, accompanied by long, thin chordae tendineae.

As a result of AV valvular insufficiency, the corresponding atria and ventricles are dilated and thickened (eccentric hypertrophy). The AV annulus is generally enlarged. *Jet lesions* (focal, thickened, fibrotic endocardial lesions) may be present and related to forceful regurgitation of blood from the ventricle to the atrium. Atrial rupture is a rare but frequently lethal end-stage finding with severe disease (Fig. 25–12). Calcification may occur in valves or the AV annulus. Pulmonary edema and pleural, pericardial, and abdominal effusions may occur.

HISTOLOGIC FEATURES. Normal AV valves are composed of four layers and have been described as follows from the atrial to ventricular aspect:[125a, 130] *atrialis,* a thin layer of endothelial cells supported by connective tissue and a thin layer of smooth muscle cells (myocytes are present in the basal third of the valve beneath the atrialis); *spongiosa,* a loose collection of collagen, fibroblasts, Anichkov's cells, and elastic fibers embedded in mucopolysaccharide-rich ground substance; *fibrosa,* a dense layer of compact collagen that continues with the annulus and central core of chordae tendineae; and *ventricularis,* structurally similar to the atrialis but lacking a layer of smooth muscle.

The histologic basis for endocardiosis is changes in the spongiosa valve layer, which include proliferation of loose tissues (increased collagen, elastic tissue, and edematous ground substance) accompanied by deposition of increased extracellular matrix. The latter contains glycosaminoglycans (GAGs), formerly known as acid mucopolysaccharide.[131] Disorders of collagen synthesis, content, or organization in humans are suggested as a cause of myxomatous transformation in cases of mitral valve prolapse.[132] However, the etiology of chronic valvular disease in dogs is unknown.

INFECTIVE (VEGETATIVE) ENDOCARDITIS

Dogs and cats may occasionally develop endocarditis involving one or more heart valves, supporting structures, or myocardium. Bacterial infection is most common,[133–140] although infections by other organisms are reported.[138] Large breed, male, older dogs are more commonly affected, and the German shepherd may be predisposed. Bacterial endocarditis is rare in the cat.[30, 31, 139]

In dogs, the mitral valve is infected most commonly, followed by the aortic valve. Involvement of the tricuspid valve is uncommon, and the pulmonic valve is rarely affected. Although preexisting valvular injury favors development of infectious endocarditis experimentally, most affected dogs do not have a history of valvular disease. Subaortic stenosis is the most common

congenital defect associated with bacterial endocarditis.[140]

GROSS FINDINGS. Vegetative masses are attached to valve endocardial surfaces, especially the ventricular aspects of the aortic valves and the atrial surfaces of the mitral valve (see Figs. 8–23; 26–2). Valve leaflets are edematous, hemorrhagic, deformed, and sometimes perforated. This predisposes to valvular insufficiency and associated chamber enlargement. Left-sided congestive heart failure and systemic evidence of sepsis are common.

HISTOLOGIC FEATURES. Valvular vegetations are composed of amorphous strands of fibrin, necrotic debris, disintegrating inflammatory cells (e.g., mononuclear cells and neutrophils), platelets, and bacteria. Necrosis of valve stroma is common. Septic emboli can seed any organ, causing associated microabscesses or infarcts. The kidney, myocardium, spleen, and left ventricle are most commonly involved (see Fig. 26–3).[134]

MYOCARDIAL DISEASES (CARDIOMYOPATHIES)

Cardiomyopathies comprise diffuse and variable myocardial diseases associated with abnormal myocardial structure or function. They may be primary (idiopathic) or may occur secondary to systemic or metabolic conditions.[30, 31, 141–148a] Myocardial disorders constitute the majority of feline heart disease (chapter 28);[13, 14, 29–31, 47, 141–143] in dogs, dilated cardiomyopathy is the second most common cause of heart failure (chronic acquired valvular disease is the most common), but hypertrophic cardiomyopathy is rare (chapter 27).[14, 143–147a]

IDIOPATHIC HYPERTROPHIC CARDIOMYOPATHY

This diverse disease entity has varied morphologic profiles.[13, 14, 141–147a] Dogs and cats share many structural similarities with idiopathic hypertrophic cardiomyopathy (HCM) as described in humans,[13, 14] including HCM with fixed and dynamic obstruction of the left ventricular outflow tract.[13, 143] The relationship between some cases of canine HCM and fixed subaortic stenosis awaits clarification.[143]

GROSS FINDINGS. Most cats have diffuse but asymmetric distribution of LV hypertrophy involving substantial portions of ventricular septum and LV free wall (see Fig. 28–6). Less commonly, segmental patterns of hypertrophy occur, often with abrupt transitions in wall thickness or involvement of noncontiguous segments (Fig. 28–7). The LV cavity is reduced and the LA is enlarged and hypertrophied.[13, 14] In dogs, the most consistent feature is marked generalized, concentric LV hypertrophy with a small cavity, often with asymmetric septal hypertrophy.[14, 145, 147]

Absolute and relative heart weights in affected animals are substantially increased.[14] Heart weight in relation to body weight is significantly greater in cats (6.4 ± 0.1 g/kg) and dogs (9.6 ± 0.3 g/kg) with HCM, compared with normal cats (mean, 4.8 ± 0.1 g/kg) and normal dogs (mean, 6.6 ± 0.3 g/kg), respectively. Necropsy of 51 HCM cats recorded a maximal ventricular septal thickness of 9.0 ± 0.2 mm (controls, 5.0 ± 0.2 mm) and an anterolateral LV free wall thickness of 9.0 ± 0.1 mm (controls, 6.0 ± 0.3 mm). In dogs, necropsy cases are limited, but comparable measurements from 10 HCM dogs were ventricular septum, 19 ± 2 mm (controls, 12 ± 0.5 mm) and LV anterolateral free wall, 18.0 ± 1.5 mm (controls, 15.0 ± 0.7 mm).[14] Focal, endocardial fibrosis is common.

In cats and dogs with dynamic LV outflow obstruction, a fibrous, mural endocardial plaque is prevalent at the basal septum in apposition to the anterior mitral valve leaflet in the left LV outflow tract. The anterior mitral valve leaflet is also thickened in these cases.[13, 143] In affected cats, pulmonary edema is present in more than half of necropsied cases, and pleural effusion is evident in about 20 percent; arterial thromboembolism occurs in a high percentage of cases (Figs. 28–28, 28–30, 28–34, 28–35) and atrial or ventricular ball thrombi are occasionally present (Figs. 28–12, 28–14, 28–15). Aneurysmal thinning of the LV apex is common.[13, 141–145]

HISTOLOGIC FEATURES. The most characteristic histologic features are bizarre, disorganized cellular architecture (see Fig. 36–4), abnormal small intramural coronary arteries (see Fig. 36–5 and Color Plate 11), and increased amounts of matrix or replacement fibrosis (see Figs. 36–4, 36–5).[13, 14, 141–147] Myocytes are hypertrophied and have large, rectangular, hyperchromic nuclei. In a series of 51 cats and 10 dogs with HCM,[14] ventricular septal myofiber disorganization was recorded from 15 (30%) cats and 2 (20%) dogs. Septal disorganization comprising 5 percent or more of relevant tissue sections was present in 14 (27%) cats and 2 dogs. Extensive myocyte disarray (≥25%) was present in 7 (14%) cats and no dogs. Cellular disorganization was predominantly type I pattern, which involved small foci of adjacent cardiac muscle cells. Abnormally thick intramural coronary arteries, usually with reduced lumens, were noted in 74 percent of cats (see Fig. 36–5) and 60 percent of dogs and were most prevalent in sections with moderate or severe fibrosis. Medial and intimal thickening was associated with increased connective tissue elements (and much less commonly, smooth muscle cells). Interstitial myocar-

dial fibrous tissue or replacement fibrosis was present in 53 percent of cats and 40 percent of dogs.

SECONDARY CAUSES OF LEFT VENTRICULAR HYPERTROPHY

Left ventricular hypertrophy can occur secondary to certain systemic and metabolic diseases. In older cats, hyperthyroidism[148] and systemic hypertension[149, 150] are common. Most cases of *thyrotoxicosis* result from functional thyroid gland adenoma (adenomatous hyperplasia) involving one or both thyroid glands (see Figs. 34–5, 34–6). In one necropsy study symmetric LV hypertrophy was common.[148] Congestive heart failure may occur but is relatively infrequent.[151] With *systemic hypertension,* hearts appear to have increased LV mass and symmetric LV hypertrophy, with minimal left atrial enlargement. Congestive heart failure is rare. Other reported associations with LV hypertrophy include hypersomatotropism (acromegaly) in cats[151a] and pheochromocytoma and hyperadrenocorticism in dogs.[138]

DILATED CARDIOMYOPATHY (DCM)

Dilated (congestive) cardiomyopathy may be primary or secondary. More than one disease process can induce associated structural and functional abnormalities.[152] Certain nutritional influences have demonstrable impact on myocardial structure and function. Of notable example is the association between feline taurine deficiency and DCM, and its reversibility with dietary taurine supplementation.[153] Whereas commercial diet reformulation largely eliminated this etiology by the beginning 1990s, taurine deficiency is still encountered in dogs and cats occasionally. Idiopathic feline myocardial failure is currently recognized but incompletely characterized.[154, 154a] A final, end-stage pathway for severe myocardial injury has been postulated for DCM,[155] and this mechanism may possibly play a role in some cats. In dogs, DCM is predominantly a disease of large and giant breeds, although cocker spaniels and other smaller breeds are occasionally affected.[142, 143, 154b] Nutritional abnormalities have been identified in some dogs, and a small number of cases of L-carnitine and taurine deficiencies have been reported.[156, 156a] However, as with cats, the etiology of most canine DCM is unknown.

GROSS FINDINGS. Classic features of DCM include severe, generalized dilation of all four cardiac chambers, ventricular wall thinning, increased end-diastolic and end-systolic volumes, and biventricular heart failure (see Figs. 27–3; 28–18).[31, 47, 141, 143] In idiopathic feline DCM, pathologic findings are more variable.[154a] Papillary muscles and ventricular trabeculae are flattened and atrophied. The heart weight of DCM cats exceeds normal but is less than that of hearts with HCM. Mitral valve complex alterations are common and may include short and thick leaflets; short, stout, long, or thin chordae tendineae; and upward malposition of papillary muscles. Tricuspid valve complex alterations may also be observed, including adhesion of the septal leaflet to the ventricular septum; direct insertion of the lateral leaflet into papillary muscles; and short, stout, long, or thin chordae tendineae. These valvular complex changes are often similar to those observed in kittens with severe atrioventricular valvular dysplasia. Thus, it may be difficult in some cases to differentiate between primary myocardial disease and end-stages of severe valvular dysplasia, or to determine the potential contribution of the latter. Endocardial fibrosis is usually mild and limited when present. Occasionally, the myocardium will be diffusely fibrotic, or focal pale, gray areas representing myocardial infarction are observed. Lesions are usually greatest in the LV. Arterial thromboembolism is common in cats but does not occur in dogs. In canine DCM there is generally little alteration in AV valve morphology.[143] Relatively unique pathologic features have been reported in some boxers, including rather mild left atrial and ventricular dilation; thickened AV valves; and, occasionally, aortic valve leaflets.[157]

HISTOLOGIC FEATURES. In cats lesions are variable. There may be some endocardial fibroelastic thickening. Inflammatory reaction is absent or scanty. Myocardial cells appear more thin, attenuated, and wavy than normal and are separated by edematous, extracellular ground substances or connective tissue.[156b] Myocytolysis is common. Myocardial fibrosis ranges from mild and focal to extensive and diffuse (Fig. 36–1; see also Fig. 27–3*B*, Color Plate 12). In dogs, extensive replacement fibrosis is uncommon.

In boxers with DCM, both active and chronic inflammations have been reported. The former includes focal myocytolysis, myonecrosis, hemorrhage, and mild mononuclear cell infiltration (e.g., macrophages, lymphocytes, plasma cells). Chronic changes are more common and include widespread myofiber atrophy, fibrosis, fatty infiltration, and fatty degeneration. These lesions are diffuse, but the RV free wall is affected earliest and most severely.[157, 158]

RESTRICTIVE AND INFILTRATIVE CARDIOMYOPATHIES

Restrictive cardiomyopathy (RCM) is the most poorly characterized feline myocardial disorder.[159, 160] Much has been extrapolated from human literature[148a, 161, 162] and remains to be verified. The hallmark of RCM is abnormal diastolic function resulting from ventricular wall stiffness that impedes diastolic fill-

ing.[161] A number of diseases have been associated with RCM in humans, including myocardial fibrosis, endomyocardial scarring, or infiltration.[148a, 162] These are variably encountered in cats but are rare in dogs. Since not all cats with pathologic myocardial changes have identifiable Doppler echo features consistent with those of humans, diagnosis is often ambiguous. Moreover, restrictive hemodynamics occur in disease states that affect the heart other than just RCM. Two-dimensional and Doppler echocardiography reveal wide phenotypic heterogeneity, as well as variability in indices of diastolic function, even among patients within certain disease categories.[148a] Unfortunately but not surprisingly, the term RCM has become a catchword for unclassified forms of myocardiopathies.

At least two different morphologic types of feline myocardial disease appear to qualify under the classification of RCM. One is characterized by left ventricular *endomyocardial fibrosis* and contains some features similar to those described in humans with Löfflers's endocarditis and endomyocardial fibrosis.[163–166] The other type is more obscure and represents a heterogeneous catchment of *idiopathic, noninfiltrative myocardial disease.* Cardiac amyloidosis is a common cause of human RCM[164] but is not a significant condition in dogs and cats.

GROSS FINDINGS. In cats with *endomyocardial fibrosis,* the heart weight is greater than normal due to moderate LV hypertrophy. Dilation and hypertrophy of the RA and RV is common. Extreme biatrial enlargement often occurs. The LA is usually most severely affected and may be hypertrophied. Pronounced, diffuse LV endocardial thickening with whitish-gray, opaque, fibrous plaquelike scar is a pathologic hallmark (Fig. 28–16). This may occur in the left ventricular outflow and inflow tracts, over the papillary muscles, chordae tendineae, and left ventricular free wall. When endocardial scarring is severe, fibrous adhesions between papillary muscles and myocardium, distortion and fusion of chordae tendineae and mitral leaflets, and occasionally obliteration of the LV cavity may occur. Mural, LA, or distal aortic thromboembolism is common.[30, 31, 142, 165, 167] In contrast, cats with *idiopathic, noninfiltrative myocardial disease* have more heterogeneous features and undoubtedly represent more than one disease process. It is grossly characterized by a relatively normal LV; the LA and often RA are moderately to severely enlarged in the absence of conditions causing volume overload or AV valve stenosis (see Fig. 28–15). The RV may become enlarged, depending on the presence and degree of pulmonary hypertension. There may be regional endocardial fibrosis but not diffuse or severe endocardial scarring. Focal myocardial wall thinning associated with infarction can be present, and left ventricular apical aneurysmal thinning is common. Mural thromboses often occur.

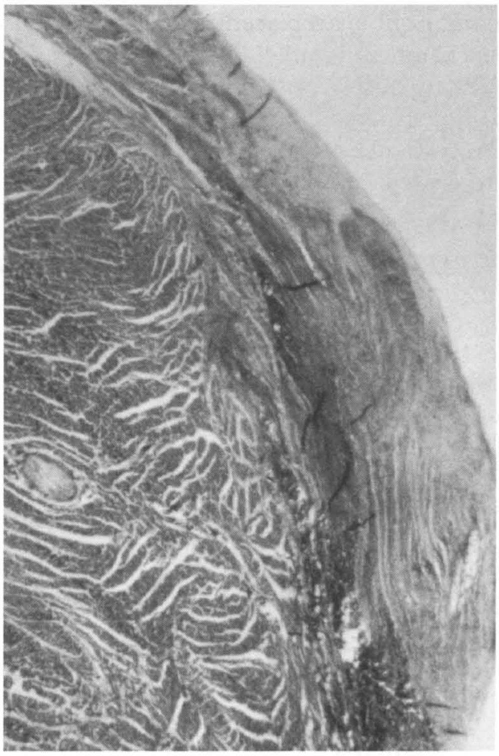


FIGURE 36–7

Histologic section of ventricular septal myocardium from a domestic cat with endomyocardial fibrosis. There is thick endocardial scar (fibrosis) and severe subendocardial fibrosis. A single abnormal narrowed intramural coronary artery is evident. Masson's trichrome stain × 100.

HISTOLOGIC FEATURES. With *endomyocardial fibrosis,* extreme endocardial thickening results from hyaline, fibrous, and granulation tissue (Fig. 36–7). The surface is covered by a layer of hyaline tissue and collagenous fibers, occasionally displaying chondroid metaplasia. Underneath is loose, cellular, fibrous tissue. Adjacent to the myocardium is granulation tissue made up of histiocytes, lymphocytes, and plasma cells. Hypertrophy of myocytes and interstitial fibroplasia are common. In the left ventricular free wall and ventricular septum, myocytolysis and arteriosclerosis may accompany severe endomyocardial fibrosis in advanced cases.[31, 167] These changes are similar but not identical to those in humans with restrictive cardiomyopathy.[148a, 162, 163] A spectrum of changes has been observed with *idiopathic, noninfiltrative myocardial disease.* Myocytes may be hypertrophied or thin with varying degrees of necrosis. Myocardial fibrosis is often diffuse and may be focally or regionally severe. Endocardial fibrosis may be patchy but is generally relatively mild.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

This newly recognized feline myocardial disease is characterized by fibrofatty infiltration of the right ven-

tricular and right atrial myocardium. Severe dilatation of these chambers is present in advanced cases (see Figs. 28–22 to 28–24). Some cats may have variable left heart pathology as well. Myocarditis and apoptosis are common, particularly with the fibrofatty form. A more complete description is contained in chapter 28.

HEART FAILURE AND ABNORMAL, EXCESSIVE LEFT VENTRICULAR MODERATOR BANDS

Moderator bands (trabeculae septomarginalis) are normally present in the feline right ventricle[168, 169] and in both canine ventricles. In cats, abnormal diffuse networks of left ventricular moderator bands have been reported in association with congestive heart failure, ventricular dilation, and hypertrophy, without breed or sex predisposition.[122] Abnormal moderator band networks have also been identified in kittens as young as 1 day old, suggesting a congenital origin.

DUCHENNE-TYPE CARDIOMYOPATHY (CANINE X-LINKED MUSCULAR DYSTROPHY)

A muscular dystrophy recorded from a small number of golden retriever dogs has striking similarities to Duchenne's muscular dystrophy in humans.[168a–c] The genetic defect results in absence of the protein dystrophin in skeletal and cardiac muscle.

GROSS FINDINGS. Clinical signs of skeletal muscle dystrophy appear at about 8 weeks of age. Most affected dogs in experimental breeding colonies die before 5 or 6 years of age, the time when congestive heart failure develops. Myocardial lesions are not grossly visible before 11 weeks of age but become evident at 6.5 months, and are extensive by 6 years of age. Focal mineralization and pale areas of myocardium may be evident. Lesions first develop in subepicardial regions of the LV free wall, LV papillary muscles, and interventricular septum but develop more slowly in the atria and RV free wall.[168a, b]

HISTOLOGIC FEATURES. Early lesions include focal myocyte degeneration and mineralization, which evolve into linear anastomosing bands of loose fibrovascular tissue and, ultimately, dense fibrous connective tissue. Commonly, myocytes vary in size, and there is increased endomysial fibrosis. Other histopathologic changes include myofilament loss, increased numbers of mitochondria, and increased myelin, cytoplasmic lipofuscin, and lipid droplets.[168a, b]

MYOCARDITIS

By definition, focal or diffuse myocarditis is diagnosed by histopathology when myocyte necrosis or degeneration or both are associated with an inflammatory infiltrate adjacent to degenerating or necrotic myocytes.[170] Many infectious agents can injure myocardial tissue and induce degeneration or inflammation.[138, 171] Frequently, the myocardium is affected secondary to generalized systemic infection or inflammation.

VIRAL MYOCARDITIS. This has received most attention associated with canine parvovirus, although at present canine parvovirus myocarditis appears to be rare. A worldwide pandemic became recognized in 1978 as a cause of peracute, fatal myocarditis.[172–175] Acute myocarditis resulted in infected pups less than 12 weeks of age; fatal chronic myocarditis manifested signs of heart failure in dogs up to 6 months old.

Gross pathologic findings included cardiac dilation, ventricular hypertrophy, pale areas throughout the ventricles with some foci of petechiae, pulmonary edema, and pleural effusion. The LA and LV were most severely affected. Histologically, 4- to 7-week-old pups affected acutely demonstrated thin myocytes separated by extracellular, edematous ground substance, histiocytes, fibroblasts, and delicate fibrous tissue. Inflammatory reactions were usually absent. Nuclei of monocytes contained single, large, distinct, homogeneous intranuclear inclusion bodies. Myocytes displayed granulation, coagulation, and cytoplasmic fragmentation. In slightly older puppies (6 to 9 weeks), extensive inflammatory reactions were observed, consisting of lymphocytes and plasma cells. Adjacent myocytes displayed cytoplasmic coagulation, granulation, fragmentation, and lysis. Inflammation subsided in juveniles (14 to 24 weeks of age) and histiocytes, fibroblasts, granulation, and fibrous connective tissue predominated. Myofibrocytes were increased in and around intramural coronary arteries. Sarcoplasmic granulation, coagulation, fragmentation, and lysis occurred in myocytes within and surrounding areas of fibrosis. Microscopic changes were most severe in the LV free wall and interventricular septum.[172]

In cats, myocarditis is rarely diagnosed. Endomyocarditis and left ventricular endomyocardial fibrosis have been reported occurring both separately and together.[165, 166] A clinical condition of endomyocarditis with concomitant congestive heart failure and high morbidity has been described but is incompletely characterized.[31, 172, 175, 176] In a necropsy series of 461 cardiomyopathic cats, about 6 percent were diagnosed histologically with endomyocarditis. Gross lesions compatible with endomyocardial fibrosis (see under restrictive cardiomyopathy) were common, suggesting a possible association with endomyocarditis in some cases.[175] Recently, viral genomic DNA has been identified in myocardium of cats with hypertrophic, restrictive, and dilated cardiomyopathy.[176a]

DIAGNOSIS. Viral myocarditis has been historically difficult to diagnose, even when endomyocardial biopsies are obtained.[170] However, molecular genetic techniques employing polymerase chain reaction analysis to identify the presence of viral nucleic acid in infected tissues and body fluids has opened up new avenues for its detection.[176a, 177]

BACTERIAL MYOCARDITIS. This is usually encountered in association with bacterial endocarditis or sepsis, although myocardial abscesses are occasionally detected at necropsy with apparently normal cardiac valves (Fig. 36–8). Histologic findings are characterized by mononuclear inflammatory cells (especially neutrophils) and bacteria (see Fig. 36–3; see also Fig. 28–27).

CANINE CHAGAS' MYOCARDITIS. This disease is caused by the protozoan parasite *Trypanosoma cruzi,* which is transmitted by an insect vector (Reduviidae). In the acute stage, evaluation of a thick blood smear may reveal the presence of circulating trypomastigotes (Fig. 36–9). Gross pathology is characterized by mild RA and RV dilation; subendocardial gray to white foci, streaks, or pale zones; and granulomatous myocarditis with pseudocysts containing amastigotes (Fig. 36–10; see also Fig. 27–14). Chronic Chagas' disease is characterized by ventricular dilation and thinning of the ventricular free walls; multifocal interstitial lymphoplasmacytic and histiocytic infiltrates; perivasculitis and marked fibrosis; and a positive indirect fluorescent antibody test.[178]

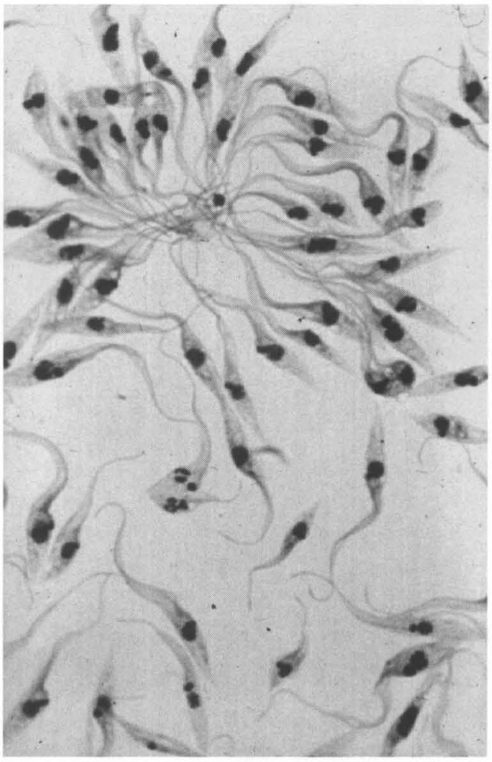


FIGURE 36–9

Photomicrograph of a thick blood smear from a dog with an acute stage of Chagas' myocarditis. Circulating trypomastigotes of *Trypanosoma cruzi* are clearly evident. (Courtesy of Dr. Matt Miller.)

OTHER INFECTIOUS AGENTS. Agents such as *viral* (e.g., canine distemper virus), *parasitic* (e.g., *Toxoplasma gondii, Hepatozoon canis*), *fungal, algae-like* (e.g., *Prototheca* spp.), *rickettsial* (e.g., *Rickettsia rickettsii, Ehrlichia canis, Bartonella elizabethae*), and *spirochetal* (e.g., *Borrelia burgdorferi*) may affect the myocardium. *Infiltrative diseases* (e.g., neoplasia), *toxic* substances (e.g., myocardial depressant factors, heavy metals, ethyl alcohol), *metabolic* diseases (e.g., chronic uremia, hypothyroidism), *chemicals* (e.g., doxorubicin), and *physical agents* (e.g.,

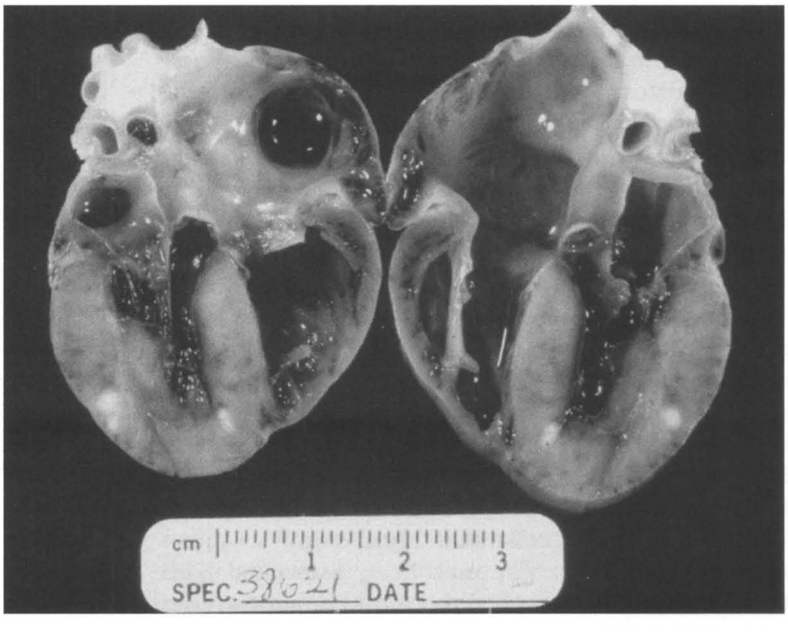


FIGURE 36–8

Gross specimen from an 8-month-old cat that died of septicemia. Notice focal whitish abscesses in the apical left ventricular free wall and ventricular septum. Abscesses were also detected in other organs. This cat also had tricuspid valve dysplasia.

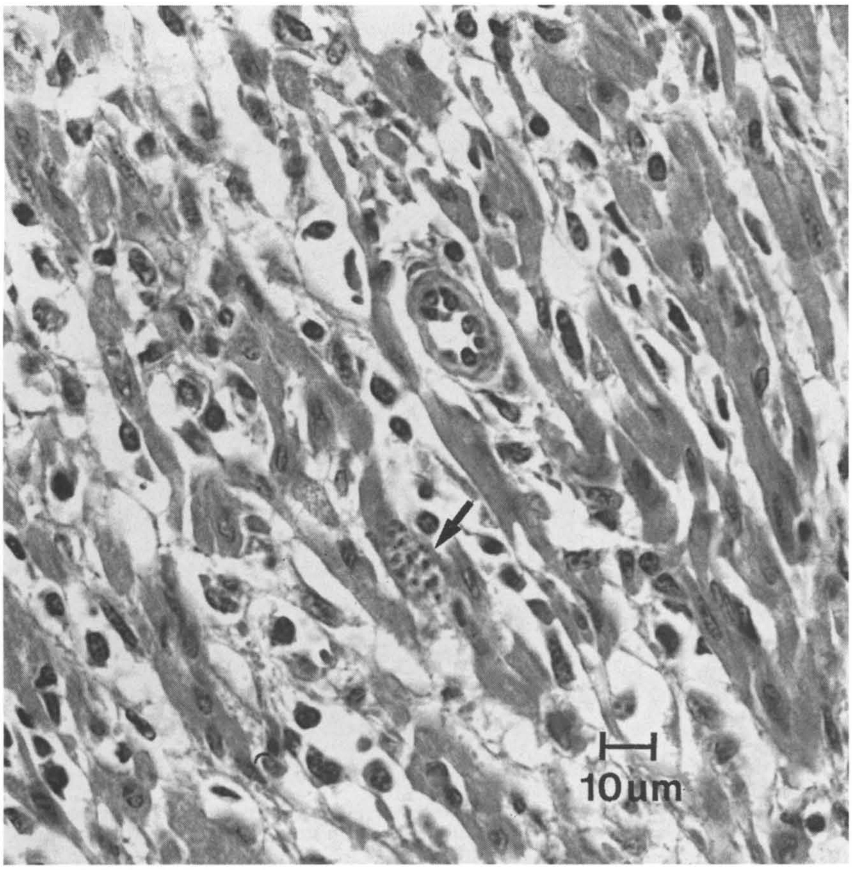


FIGURE 36–10

Photomicrograph of myocardium from a dog with acute Chagas' myocarditis. Notice a myocyte *(arrows)* containing intracellular amastigotes of *Trypanosoma cruzi*. Mononuclear leukocytic inflammatory cells (lymphocytes, neutrophils, plasma cells) are also present. H& E stain. (Courtesy of Dr. Kathryn Meurs.)

heat stroke) can cause myocardial degeneration or inflammation.[138, 162, 170, 171, 175]

THROMBOEMBOLIC DISEASE

Thrombus refers to clot formation (platelets, fibrin, coagulation factors, and cellular components) in the heart or vessels. An *embolus* results from migration of all or part of a clot or other material (e.g., tumor fragment, air, fat, bacteria, parasites, or foreign body). Thrombosis may result from tissue (endothelial) injury; circulatory stasis or turbulence; or hypercoagulable state.[179, 180]

SYSTEMIC THROMBOEMBOLISM. Arterial thromboembolism is a well-recognized complication of feline cardiomyopathies and has been reported in up to 48 percent of myopathic cats at necropsy.[30, 31, 142] Distal aortic saddle emboli occur in more than 90 percent of affected cats (see Figs. 28–28, 28–30, 28–34, 28–35). Brachial, renal, and mesenteric arteries represent other recognized sites for emboli. Mural thrombi are occasionally present in the left atrium or ventricle (see Figs. 28–12, 28–14, 28–15). Ischemic neuromyopathy results when distal arterial occlusion and vasoactive chemicals (e.g., serotonin) reduce collateral circulation.[181] Canine myocardial diseases have not been associated with thromboembolism. In dogs, the most common causes include bacterial endocarditis and dirofilariasis;[182] nephrotic syndrome, amyloidosis, and hypoadrenocorticism have also been reported.[183, 184]

PULMONARY THROMBOEMBOLISM (PTE). Dirofilariasis is the most commonly recognized cause (Fig. 36–11); nephrotic syndrome, renal amyloidosis, pancreatitis, immune-mediated hemolytic anemia, neoplasia, hyper-

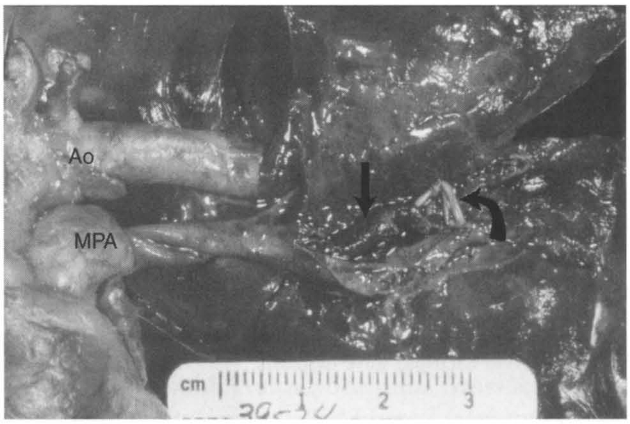


FIGURE 36–11

Heart and lungs from a dog with severe heartworm disease that died after adulticide therapy. The pulmonary artery is dissected to reveal an extensive thrombus *(straight arrow)* and adult heartworm fragments *(curved arrow)*. Ao, descending aorta; MPA, main pulmonary artery.

adrenocorticism, disseminated intravascular coagulation, and pancreatitis are other associated conditions.[184–189] PTE is a significant disease in dogs, in which it is generally underdiagnosed, although in cats, it is rarely detected. Severe PTE may cause significant ventilation-perfusion abnormalities, resulting in pulmonary hypertension or respiratory failure.

VENOUS THROMBOEMBOLISM. Although common in humans, clinically significant venous thrombosis is relatively rare. Vasculitis and thrombophlebitis may result from venous catheter placement or perivascular drug administration. *Varicosis* can accompany arteriovenous fistulas. Venous perforation or blunt trauma is usually well tolerated. Tumors may result in venous invasion, especially chemodectoma, adrenal tumors, and hemangiosarcoma.[182]

HEARTWORM DISEASE

Heartworm disease is widely distributed in the United States and many regions of Europe and Asia. Pathology is partly related to the number of adult heartworms. High heartworm burdens generally cause more severe pulmonary hypertension, thromboembolism, and a propensity to develop caval syndrome.

GROSS FINDINGS. When pulmonary hypertension is present, moderate to severe RV hypertrophy and enlargement usually develop (see Figs. 30–9; 31–5). Pneumonitis, pulmonary granuloma formation (see Fig. 30–11), pulmonary endarteritis, and pulmonary thromboembolism (see Fig. 36–11) may be observed. Caudal and accessory lobar arteries dilate, become tortuous, develop aneurysms, and lose their normal tapering arborization. Large numbers of worms mechanically obstruct blood flow (see Figs. 30–4, 30–6; 31–3, 31–4). Extracardiac signs of right-sided congestive heart failure may be present.

HISTOLOGIC FEATURES. Heartworms in pulmonary arteries produce endothelial swelling, widened intercellular junctions, sloughing of longitudinal strips of endothelium, and adhesion of activated leukocytes and platelets to sites of injury (see Figs. 30–1 to 30–3). Pulmonary arterial villi are formed by activated smooth muscle cells and collagen. Endothelial lesions and villous proliferation are most severe in caudal and accessory lung lobes.[190–192] After adulticidal therapy, embolization of worms and their fragments may cause severe pulmonary lesions, including pulmonary arterial thrombosis and granulomatous inflammation.[193, 194] Immune-mediated occult infections may result in allergic pneumonitis and pulmonary eosinophilic granulomatosis.

PERICARDIAL DISEASE

CONGENITAL PERICARDIAL DEFECTS. Congenital pericardial defects are rare and represent small or large perforations in the pericardium (see Fig. 29–2). They are usually incidental findings at necropsy. Large defects have the potential to cause cardiac herniation (see Fig. 29–3) with severe consequences. *Peritoneopericardial diaphragmatic hernias* (PPDH) are the most common congenital pericardial malformation[29] (see Figs. 29–4 to 29–6) and may be accompanied by other abnormalities (cranial abdominal hernia, sternal deformities) and congenital heart defects (ventricular septal defect).[195] Traumatic PPDH is also encountered in dogs and cats. Abdominal viscera may be found within the pericardial sac, sometimes with pericardial effusion or fibrinous tags involving viscera, endocardium, or pericardium. Intrapericardial cysts have been reported[196] (see Figs. 29–7, 29–8) and represent cystic hematomas that develop in fatty tissues that become entrapped in a small peritoneopericardial diaphragmatic hernia.

PERICARDIAL EFFUSIONS. Pericardial disease is often accompanied by accumulation of variable quantities of pericardial effusion. When it develops rapidly, increased intrapericardial pressure and decreased right-sided heart filling (cardiac tamponade) may result in secondary abdominal and pleural effusion. Effusions are categorized according to fluid characteristics (transudate-hydropericardium; exudate-pericarditis; hemorrhage-hemopericardium).[197] Cytologic evaluation can identify chylous, suppurative, or mycotic pericardial effusions but are generally unreliable to differentiate neoplastic from idiopathic effusions.[198] Hemangiosarcoma and chemodectoma, tumors that are commonly enclosed within the pericardium of dogs, and cardiac lymphoma of cats, seldom exfoliate into the effusion. Echocardiography may help identify associated cardiac or mediastinal masses (see Fig. 8–25). Chronic pericardial effusion may contain exfoliated reactive mesothelial cells that normally line the pericardium (Fig. 36–12). These can be readily misinterpreted on cytology as neoplasia, especially mesothelioma.[199]

PERICARDITIS. Infective pericarditis is uncommon in dogs and cats, but it may occur from bacterial or fungal pathogens.[197] In cats, feline infectious peritonitis has been a reported cause of pericarditis in cats.[200] With bacterial infections particularly, the pericardium may be thickened and contain a shaggy, fibrinopurulent exudate; the epicardium is infiltrated by polymorphonuclear leukocytes. Pericardial exudate may be serosanguineous or turbid and fibrinous and is frequently

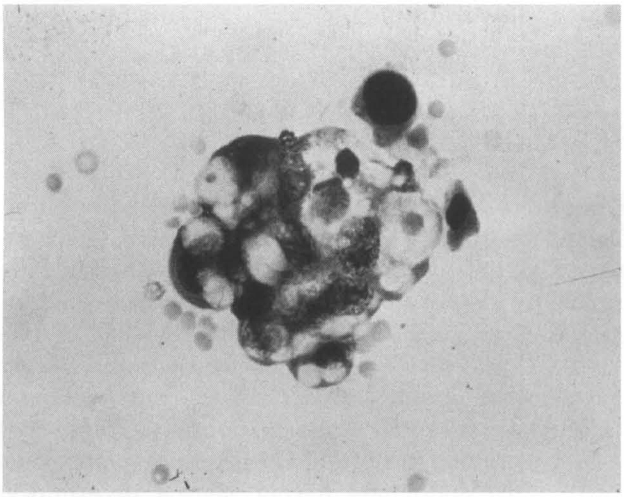


FIGURE 36–12

Cytologic specimen of pericardial fluid from a dog with idiopathic pericardial effusion. Notice the cluster of mesothelial cells characterized by moderate pleomorphism; moderate, finely granular to vacuolated basophilic cytoplasm; a central nucleus that exhibits coarsely clumped chromatin; and secretory vacuoles in some of the cells. Normally, mesothelial cells are more uniform in appearance and exhibit an eosinophilic corona. Reactive mesothelial cells may be difficult to distinguish from carcinoma cells. × 400. (Courtesy of Dr. Matt Miller.)

tenacious and purulent. Adhesions may occur that obliterate the pericardial space.

NEOPLASIA. In cats, lymphosarcoma, the most common hematopoietic feline tumor, is also the most common cardiac tumor (Fig. 28–26). Many cases are associated with feline leukemia virus infection (FeLV), but feline immunodeficiency virus (FIV) may also have a role in lymphomagenesis. Lymphosarcoma rarely involves the pericardium directly (see Figs. 29–11*B*, 29–19). In dogs, hemangiosarcoma (see Figs. 29–9*A,B*, 29–18*B*) and chemodectoma (see Figs. 29–16, 29–18*A*) are the most common tumors enclosed within the pericardial sac. Pericardial mesothelioma with pericardial effusion is described infrequently (see Fig. 29–10). Immunohistochemical staining helps differentiate mesothelioma from carcinoma.[201]

MISCELLANEOUS CARDIOVASCULAR DISEASES AND CONDITIONS

CONDUCTION SYSTEM LESIONS

Arrhythmias, syncope, and sudden death have been reported with a variety of acquired conduction system lesions. Associated conditions include infections, inflammatory diseases, and cardiomyopathies.[30, 31, 141, 202] Terminal narrowing of small arteries in the region of the conducting system may cause degenerative changes, and hereditary factors may be involved in some cases.[203] A series of Doberman pinschers with sudden death and AV nodal degeneration has been reported.[204] However, in Doberman pinschers and other dogs of various ages, chondroid metaplasia of the central fibrous body and aortic root was recorded as a normal occurrence in large-breed dogs.[204a] Conduction system abnormalities have been detected in cardiomyopathic cats from 6 months to 16 years of age. Histologic changes included degeneration and fibrosis of the AV node and degeneration and infiltration by fibrous granulation tissue of the left and right bundle branches.[31, 172]

INHERITED SUDDEN CARDIAC DEATH IN GERMAN SHEPHERDS

Inherited ventricular arrhythmias and sudden death have recently been reported in German shepherd dogs without evidence of cardiomyopathy or heart failure.[32] Death is most common between 4 and 8 months of age and frequently occurs during sleep or during rest following exercise. No gross or histologic lesions have been identified.

PERSISTENT ATRIAL STANDSTILL (SILENT ATRIA, ATRIOVENTRICULAR MYOPATHY)

A rare, acquired, progressive myopathy of dogs and cats involves severe atrial enlargement and thinning, with subsequent ECG changes of persistent atrial standstill, although complete heart block and other arrhythmias have been recorded. Congestive heart failure was present in some animals. A potential predisposition was suggested for English springer spaniels and Siamese cats.[205, 205a] Clinical and pathologic findings of humans with persistent atrial standstill[206] bore a resemblance to those of affected dogs. Reported animals were subdivided into three categories based upon clinical signs, which included long-standing cardiomyopathy (especially the dilated form in cats); muscular dystrophy (fascioscapulohumeral type); and an idiopathic condition without evidence of other pathology. It is not clear whether these clinical associations represent unique conditions or different disease stages.

GROSS FINDINGS. Atria are greatly enlarged and paper-thin with little visible muscle (Fig. 36–13). Skeletal muscle wasting was a feature observed in affected dogs but not cats. In the latter, dilated cardiomyopathy with atrial hypoplasia was recorded in necropsied cats. Ascites and pleural effusion were variably present.[205]

HISTOLOGIC FEATURES. Atrial changes include myofiber necrosis, replacement fibrosis, fibroelastosis, and fatty infiltration (Fig. 27–13). Ventricular involvement is more variable. In dogs with skeletal muscular dystro-

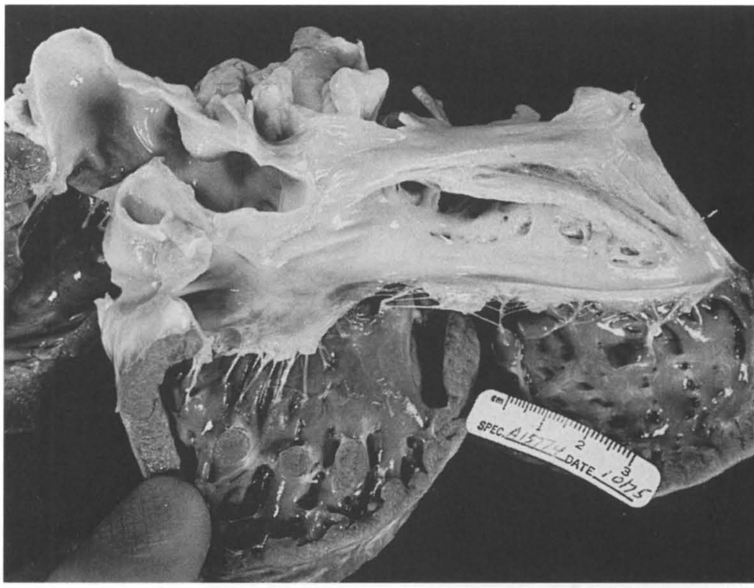


FIGURE 36–13

Right side of the heart from a 3.5-year-old male English springer spaniel with persistent atrial standstill. The right atrium is extremely dilated, with severe membranous thinning. The right ventricle is also dilated. Histology revealed replacement of right atrial myocytes with fibrous connective and adipose tissues.

phy, skeletal muscles were hyalinized, with degenerating muscle fibers and mild to moderate fatty infiltration. Skeletal muscle biopsies (upper forearm and scapular region) in most affected dogs with severe muscle atrophy were compatible with a fascioscapulohumeral type of dystrophy.[205]

GLYCOGEN STORAGE DISEASE

A heritable deficiency in Lapland dogs of lysosomal acid alpha-glucosidase causes cardiac and skeletal myopathies due to glycogen accumulation.[206a,b] Pathologic changes included cardiac enlargement with focal myocarditis and extensive glycogen infiltration.

CORONARY ARTERY DISEASE

The pathology of canine coronary artery disease has been reviewed.[38, 207–215] Disease of extramural coronary arteries is quite uncommon in dogs[207, 211, 213–216] and cats.[213] A number of dogs with *atherosclerosis* associated with hypothyroidism have been documented.[212–214] Stenosis of extramural coronary arteries caused by fibroelastic intimal thickening, discontinuity of internal elastic lamella, and focal atrophy of medial smooth muscle was reported in two adult Labrador retrievers.[211] In contrast, narrowing of small intramural coronary arteries is relatively common in aged dogs with chronic mitral valve endocardiosis (caused by musculoelastic intimal thickening, intimal cushions, microthrombi, hyalinosis, and amyloidosis);[207–209] in dogs with congenital subaortic and pulmonic stenosis (caused by arteriosclerosis);[38, 208, 215] and in dogs and cats with idiopathic hypertrophic cardiomyopathy (see Fig. 36–5) (caused by increased connective tissue elements and smooth muscle cell proliferation of the media and intima).[13, 14, 144, 145] *Necrotizing polyarteritis* is a rare idiopathic disease reported to affect extramural and intramural coronary arteries.[216] Arteriosclerosis thought to be associated with systemic hypertension has been reported in cats, including idiopathic arterial mineralization involving a variety of arteries.[217–219] Its bearing, if any, on coronary arteries is unclear.

MYOCARDIAL INFARCTION

Myocardial infarction is uncommonly reported in dogs and cats but does occur in a number of diverse, although often poorly characterized, settings.[207–210, 213, 215, 220, 221, 221a] Whereas most infarctions in humans result from coronary atherosclerosis with superimposed coronary thrombosis, canines and felines usually have nonatheromatous coronary artery disease.

In felines, myocardial infarction is frequently observed at necropsy to be associated with cardiomyopathies.[213, 215, 220] In hypertrophic cardiomyopathy with thromboembolism, infarction has been noted at the LV apex (Fig. 36–14) and may involve the papillary muscles; occasional extramural coronary arterial thrombosis has also been recognized in these cases.[213] In addition, cases of idiopathic myocardial failure, restrictive cardiomyopathy, and unclassified myocardial diseases have been observed with regions of infarcted LV posterior wall at the papillary muscle level (Fig. 36–15).

In dogs, myocardial infarction (especially microscopic) has been observed in a variety of conditions. These include in the hearts of old dogs with degenerative valvular disease, in subaortic stenosis, in occasional myocardial disorders, and secondary to noncardiac conditions, including sepsis and pulmonary neoplasia.

GROSS FINDINGS. Infarction appears grossly as focal, dark gray, or pale myocardium. Atherosclerosis is a

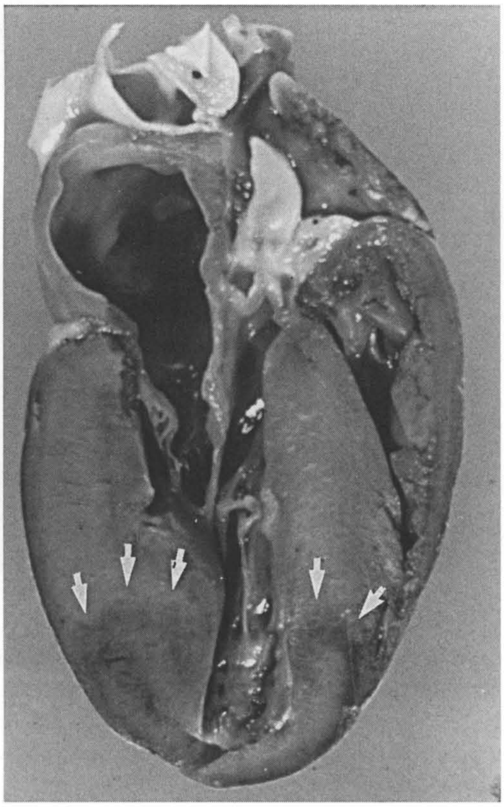


FIGURE 36–14

A heart transected in the long axis of a cat with hypertrophic cardiomyopathy and sudden death. A large, acute myocardial infarct encompasses the apical third of the hypertrophied left ventricle, appearing darker than adjacent myocardium. Arrows delineate the border of infarcted myocardium.

rare finding, but affected animals may have yellow-white, dilated, and tortuous coronary arteries with adjacent irregular, dull foci of infarcted myocardium (see Fig. 33–4).[207, 212] With coronary amyloidosis and myocardial necrosis, gross changes are nonspecific, but the LV may contain focal or diffuse pale infarcted areas associated with variable degrees of coronary arterial occlusion.[127, 207, 213, 214] In some dogs the origin of coronary emboli has been associated with neoplastic tissue from the lungs.[208] Others have reported that dogs with septicemia[222] or vegetative endocarditis and coronary vasculitis had coronary thromboembolism and hemorrhagic necrosis of adjacent myocardium.[127, 215, 220, 223] In dogs with severe right or left ventricular pressure overload from pulmonic or aortic stenosis, respectively, circular myocardial necrosis may occur as a concentric, pale, dull, or dark purple region involving subendocardial portions of hypertrophied ventricular myocardium, including papillary muscles and trabeculae carneae.[215, 220]

HISTOLOGIC FEATURES. In general, infarcted myocardium reveals myocyte streaking and waviness; sarcoplasmic coagulation, vacuolization, and fragmentation; contraction bands; myocytolysis and fragmentation. There is excessive extracellular ground substance and occasional extravasation of erythrocytes separating affected myocytes. Atherosclerotic, thromboembolic, amyloid, or vasculitic coronary arteries are usually enclosed in adjacent necrotic myocardium. Contraction bands, fragmentation, and vacuolization of sarcoplasm with or without extravasation of erythrocytes in and around the affected myocytes is observed in circular myocardial necrosis, with minimal coronary artery changes. In cases of severe feline hypertrophic cardiomyopathy, focal interstitial or massive myocardial fibrosis and acute vacuolar and/or coagulative necrosis may occur. Abnormal coronary arteries characterized by thickened walls and decreased luminal size occurred in about one third of affected hearts.[127, 207–210, 213–215, 220, 221] In old dogs with chronic acquired valve disease, myocardial necrosis and fibrosis in the presence of intramural coronary artery diseases is a commonly reported microscopic finding, presumably re-

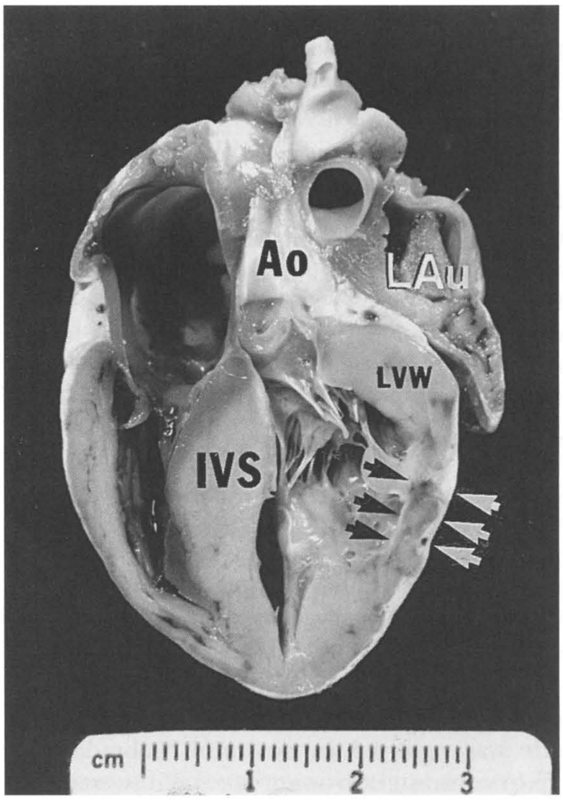


FIGURE 36–15

A heart transected in the long axis from a 15-year-old male domestic short-hair cat with myocardial failure. Necropsy measurement of the interventricular septum (IVS) was approximately 9 mm, and the basal LV free wall (LVW) was 7.5 mm. Notice the dramatic segmental thinning of the LV free wall, which measured 3 mm between the arrows (contrast this to the thicker contiguous basal and apical wall segments). Echocardiographic imaging showed this thinned segment to be severely hypokinetic. This region was characterized histologically by replacement fibrosis associated with a chronic transmural myocardial infarction. Ao, aortic root; LAu, left auricle.

sulting from focal ischemia caused by narrowing of affected intramural arteries.[127, 207, 210, 221] Microscopic intramural myocardial infarction (MIMI) in these hearts had been reported in early literature[224] but has received little attention in the past 3 decades.

AGE AND THE CARDIOVASCULAR SYSTEM

Age-associated changes have been well documented in the human cardiovascular system and could influence diagnosis and treatment in certain geriatric patients.[225–228] Increased LV wall thickness has been reported to involve the interventricular septum in one study[226] and the LV posterior wall in another,[227] although overall cardiac size did not change. Mean heart weights progressively increased, then declined in very old age. Mean valve circumferences increased progressively with age. In the myocardium, increased myocyte size with age-associated loss of myocytes occurs. Degenerative changes include lipid deposition; tubular dilation; lipofuscin deposition; decreased mitochondrial oxidative phosphorylation; delayed protein synthesis; a decreased number of SA nodal cells (AV node and His bundle show less change); and a slight increase in elastic tissue, fat, collagen, and fibrotic foci.[228] In the AV conduction system of large breed dogs over 5 years of age, increased fibrous connective tissue, infiltration of adipose tissue, loss of conduction fibers, and focal fibrosis extending from the central fibrous body have been documented. Thickened medial and intimal proliferation in small intramural coronary arterioles supplying the AV node were detected in half of these dogs.[204a] A profound age-related decrease in cardiac β-adrenergic responsiveness (including down regulation, decreased agonist binding of β-1 receptors, uncoupling of β-2 receptors, and abnormal G protein–mediated signal transduction) has been reported in humans[229] and in animal models. Systolic function in humans is well preserved, but diastolic filling is dramatically altered by aging, with elderly subjects exhibiting a doubling of percent atrial contribution to ventricular filling.[227]

References

1. Isner JM. The cardiologist as clinician and pathologist: the interactions of both and the limitations of each. *In* Virmani R, Atkinson JB, Fenoglio JJ (eds). Cardiovascular Pathology. Philadelphia, WB Saunders, 1991, p 21
2. Opie LH. The Heart, 2nd ed. New York, Raven Press, 1991, p 369
3. Katz AM. The cardiomyopathy of overload: an unnatural growth response in the hypertrophied heart. Ann Intern Med 121:363, 1994
4. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 56:56, 1975
5. Ross J Jr. Adaptations of the left ventricle to chronic volume overload. Circ Res 35 (suppl 2):64, 1974
6. Jennings RB, Ganote CE. Structural changes in myocardium during acute ischemia. Circ Res 35 (Suppl 3): 156, 1974
7. Schoen FJ. The heart. *In* Cotran RS, Kumar V, Robbins SL (eds). Pathologic Basis of Disease. 5th ed. Philadelphia, WB Saunders, 1994, p 538
8. Thompson HJ, Strange R, Schedin PJ. Apoptosis in the genesis and prevention of cancer. Cancer Epidem Biomarkers Prev 1:597, 1992
9. Sharov VG, Sabbah HN, Shimoyama H, et al. Evidence of cardiocyte apoptosis in myocardium of dogs with chronic heart failure. Am J Pathol 148:141, 1996
10. Narula J, Haider N, Virmani R, et al. Apoptosis in myocytes in end-stage heart failure. N Engl J Med 335:1182, 1996
11. Weber KT. The healing wound: a case for extracellular matrix. Heart Failure Rev 1:53, 1996
12. Sappino AP, Schürch W, Gabbiani G. Differentiation repertoire of fibroblastic cells: expression of cardioskeletal proteins as marker of phenotypic modulations. Lab Invest 63:144, 1990
13. Fox PR, Liu SK, Maron BJ. Echocardiographic assessment of spontaneously occurring feline hypertrophic cardiomyopathy. An animal model of human disease. Circulation 92:2645, 1995
14. Liu SK, Roberts WC, Maron BJ. Comparison of morphologic findings in spontaneously occurring hypertrophic cardiomyopathy in humans, cats and dogs. Am J Cardiol 72:944, 1993
15. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. Circulation 83:1849, 1991
16. Sun Y, Weber KT. Fibrosis and myocardial ACE: possible substrate and independence from circulating angiotensin II. J Cardiac Failure 1:81, 1994
17. Mukherjee D, Sen S. Collagen phenotypes during development and regression of myocardial hypertrophy in spontaneously hypertensive rats. Circ Res 67:1474, 1990
18. Bishop J, Greenbaum J, Gibson D, et al. Enhanced deposition of predominantly type I collagen in myocardial disease. J Mol Cel Cardiol 22:1157, 1990
19. Caulfield JB, Borg TK. The collagen network of the heart. Lab Invest 40:364, 1979
20. Robinson TF. Structural arrangement of myocytes and fibrillar connective tissue in heart muscle. *In* Robinson TF, Kinne RKH (eds). Cardiac Myocyte–Connective Tissue Interactions in Health and Disease. Issues in Biomedicine. Vol 13. Basel, Karger, 1990, p 53
21. Factor SM. Pathologic alterations of myocyte–connective tissue interactions in cardiovascular disease. *In* Robinson TF, Kinne RKH (eds). Cardiac Myocyte–Connective Tissue Interactions in Health and Disease. Issues in Biomedicine. Vol 13. Basel, Karger, 1990, p 130
22. Dungworth DL. The respiratory system. *In* Jubb KVF, Kennedy PC, Palmer N (eds). Pathology of Domestic Animals. 4th ed, Vol 2. San Diego, Academic Press, 1993, p 539
23. Wilkins RJ. Clinical pathology of feline cardiac disease. Vet Clin North Am 7:285, 1977
24. Sherding RG. Diseases of the pleural cavity. *In* Sherding RG (ed). The Cat; Diseases and Clinical Management. 2nd ed. New York, Churchill Livingstone, 1994, p 1053
25. Fossum TW, Forrester SD, Swenson CL, et al. Chylothorax in cats: 37 cases (1969–1989). J Am Vet Med Assoc 198:672, 1991

26. Kelly WR. The liver and biliary system. *In* Jubb KVF, Kennedy PC, Palmer N (eds). Pathology of Domestic Animals. 4th ed, Vol 2. San Diego, Academic Press, 1993, p 319
27. Perloff JK. The Clinical Recognition of Congenital Heart Disease. 4th ed. Philadelphia, WB Saunders, 1994
28. Bonagura JD, Darke PGG. Congenital heart disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed. Philadelphia, WB Saunders, 1995, p 892
29. Buchanan JW. Causes and prevalence of cardiovascular disease. *In* Kirk RW, Bonagura JD (eds). Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1992, p 647
30. Harpster NK. The cardiovascular system. *In* Holzworth J (ed). Diseases of the Cat. Vol 1. Philadelphia, WB Saunders, 1987, p 820
31. Liu SK. Pathology of feline heart disease. Vet Clin North Am 7:322, 1977
32. Moïse NS, Meyers-Wallen V, Flahive WJ, et al. Inherited ventricular arrhythmias and sudden death in German shepherd dogs. J Am Coll Cardiol 24:233 1994
33. Lehmkuhl LB, Bonagura JD. Canine subvalvular stenosis. *In* Bonagura JD (ed). Kirk's Current Veterinary Therapy. Vol XII. Philadelphia, WB Saunders, 1995, p 822
34. Pyle RL, Peterson DF, Chacko S. The genetics and pathology of discrete subaortic stenosis in the Newfoundland dog. Am Heart J 92:324, 1976
35. Harpster NK. Cardiovascular diseases of the domestic cat. Adv Vet Sci Comp Med 2:39, 1977
36. Stepien RL, Bonagura JD. Aortic stenosis: clinical findings in six cats. J Small Anim Pract 32:341, 1991
37. Patterson DF. Congenital defects of the cardiovascular system of dogs: studies in comparative cardiology. Adv Sci Comp Med 20:1, 1976
38. Flickinger GL, Patterson DF. Coronary lesions associated with congenital subaortic stenosis in the dog. J Pathol Bacteriol 93:133, 1967
39. Pyle RL, Lowensohn HS, Khouri EM, et al. Left circumflex coronary artery hemodynamics in conscious dogs with congenital subaortic stenosis. Circ Res 33:34, 1973
40. Fingland RB, Bonagura JD, Myer CW. Pulmonic stenosis in the dog: 29 cases (1975–1984). J Am Anim Hosp Assoc 189:218, 1986
41. Eyster GE. Pulmonic stenosis. *In* Bojrab MJ (ed). Current Techniques in Small Animal Surgery. 2nd ed. Philadelphia, WB Saunders, 1983, p 462
42. Patterson DF, Haskins ME, Schnarr WR. Hereditary dysplasia of the pulmonary valve in beagle dogs. Am J Cardiol 47:631, 1981
43. Hawe RS: Pulmonic stenosis in a cat. J Am Anim Hosp Assoc 17:777, 1981
44. Tashjian RJ, Das KM, Palich WE, et al. Studies on cardiovascular disease in the cat. Ann NY Acad Sci 127:581, 1965
45. Fox PR. Congenital feline heart disease. *In* Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 391
46. Bolton GR, Liu SK. Congenital heart disease in the cat. Vet Clin North Am 7:341, 1977
47. Liu SK. Cardiovascular pathology. *In* Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 641
48. Buchanan JW. Pulmonic stenosis caused by single coronary artery in dogs: four cases (1965–1984). J Am Vet Med Assoc 196:115, 1990
49. Fox PR, Miller MW, Liu SK. Clinical, echocardiographic, and Doppler imaging characteristics of mitral valve stenosis in 2 dogs. J Am Vet Med Assoc 201:1575, 1993
50. Lehmkuhl LB, Ware WA, Bonagura JD. Mitral stenosis in 15 dogs. J Vet Intern Med 8:2, 1994
51. Stamoulis ME, Fox PR. Mitral valve stenosis in three cats. J Small Anim Pract 34:452, 1993
52. Brown WA, Thomas WP. Balloon valvuloplasty of tricuspid stenosis in a Labrador retriever. J Vet Intern Med 9:419, 1995
53. Lord PF, Liu SK, Carmichael JA. Congenial tricuspid stenosis with right ventricular hypoplasia in a cat. J Am Vet Med Assoc 153:300, 1968
54. Tobias AH, Thomas WP, Kittleson MD, et al. Cor triatriatum dexter in two dogs. J Am Vet Med Assoc 220:285, 1993
55. Jevens DJ, Johnston SA, Jones CA, et al. Cor triatriatum dexter in two dogs. J Am Anim Hosp Assoc 29:289, 1993
56. Miller MW, Bonagura JD, DiBartola SP, et al. Budd-Chiari–like syndrome in two dogs. J Am Anim Hosp Assoc 25:277, 1989
57. MacIntire DK, Henderson RH, Banfield C, et al. Budd-Chiari–like syndrome in a kitten, caused by membranous obstruction of the caudal vena cava. J Am Anim Hosp Assoc 31:484, 1995
58. Gordon B, Trautvetter E, Patterson DF. Pulmonary congestion associated with cor triatriatum in a cat. J Am Vet Med Assoc 180:75, 1982
59. Patterson DF, Pyle RL, Buchanan JW, et al. Hereditary patent ductus arteriosus and its sequelae in the dog. Circ Res 29:1, 1971
60. Detweiler DK, Patterson DF. Prevalence and types of cardiovascular disease in dogs. Ann NY Acad Sci 127:481, 1965
61. Eyster GE, Eyster JT, Cord GB, et al. Patent ductus arteriosus in the dog: characteristics of occurrence and results of surgery in one hundred consecutive cases. Am J Vet Res 168:435, 1976
62. Pyle RL, Park RD, Alexander AF, et al. Patent ductus arteriosus with pulmonary hypertension in the dog. J Am Vet Med Assoc 178:565, 1981
63. Patterson DF, Detweiler DK. Hereditary transmission of patent ductus arteriosus in the dog. Am Heart J 74:289, 1967
64. Weirich WE, Blevins WE, Rebar AH, et al. Late consequences of patent ductus arteriosus in the dog: a report of six cases. J Am Anim Hosp Assoc 14:40, 1978
65. Ackerman NA, Burk R, Hahn AW, et al. Patent ductus arteriosus in the dog: a retrospective study of radiographic, epidemiologic, and clinical findings. Am J Vet Res 39:1805, 1978
66. Patterson DF. Epidemiologic and genetic studies of congenital heart disease in the dog. Circ Res 23:171, 1968
67. Patterson DF. Canine congenital heart disease: epidemiology and etiological hypotheses. J Small Anim Pract 12:263, 1971
68. Jones, CL, Buchanan JW. Patent ductus arteriosus: anatomy and surgery in a cat. J Am Vet Med Assoc 179:364, 1981
69. Jeraj K, Ogburn P, Lord P, Wilson JW. Patent ductus arteriosus with pulmonary hypertension in a cat. J Am Vet Med Assoc 172:1432, 1978
70. Cohen JS, Tilley LP, Liu SK, DeHoff WD. Patent ductus arteriosus in five cats. J Am Anim Hosp Assoc 11:95, 1975
71. Buchanan JW. Patent ductus arteriosus. Semin Vet Med Surg (Small Anim) 9:168, 1994
72. Eyster GE, Dalley JB, Chaffee A, et al. Aorticopulmo-

nary septal defect in a dog. J Am Vet Med Assoc 167:1094, 1975
73. Buchanan JW. Morphology of the ductus arteriosus in fetal and neonatal dogs genetically predisposed to patent ductus arteriosus. Birth Defects 14:349, 1978
74. Eyster GE. Atrial and ventricular septal defects. Semin Vet Med Surg (Small Anim) 9:227, 1994
75. Tashjian RJ, Das KM, Palich WE, et al. Studies on cardiovascular disease in the cat. Ann NY Acad Sci 127:581, 1965
76. Liu SK, Ettinger SJ. Persistent common atrioventricular canal in two cats. J Am Vet Med Assoc 153:556, 1968
77. Troy GC, Turnwald GH. Atrial fibrillation and abnormal ventricular conduction presented as right bundle branch block in a dog with an atrial septum primum defect. J Am Anim Hosp Assoc 15:417, 1979
78. Eyster GE, Anderson LK, Krenbeil JD, et al. Surgical repair of atrial septal defect in the dog. J Am Vet Med Assoc 169:1081, 1976
79. Pyle RL, Patterson DF. Multiple cardiovascular malformations in a family of Boxer dogs. J Am Vet Med Assoc 160:965, 1972
80. Hamlin RL, Smith CR, Smetzer DL. Ostium secundum-type interatrial septal defects in the dog. J Am Vet Med Assoc 143:149, 1963
81. Jeraj K, Ogburn PN, Johnston GR, et al. Atrial septal defect (sinus venosus type) in a dog. J Am Vet Med Assoc 177:342, 1980
82. Anderson RH. New light on morphogenesis of atrioventricular septal defects. Int J Cardiol 18:79, 1988
83. Wenick ACG, Zevallos J. Developmental aspects of atrioventricular septal defects. Int J Cardiol 18:65, 1988
84. Hamlin RL, Smetzer DL, Smith CR. Interventricular septal defects (Roger's disease) in the dog. J Am Vet Med Assoc 145:331, 1964
85. Sisson D, Luethy M, Thomas WP. Ventricular septal defect accompanied by aortic regurgitation in five dogs. J Am Anim Hosp Assoc 27:441, 1995
86. Ware WA, Bonagura JD. Multiple congenital cardiac anomalies and Eisenmenger's syndrome in a dog. Compend Small Anim Med Pract Vet 10:932, 1988
87. Turk JR, Miller JB, Sande RD. Plexogenic pulmonary arteriopathy in a dog with ventricular septal defect and pulmonary hypertension. J Am Anim Hosp Assoc 18:608, 1982
88. Nimmo-Wilkie JS, Feldman EC. Pulmonary vascular lesions associated with congenital heart defects in three dogs. J Am Anim Hosp Assoc 17:485, 1981
89. Patterson DF, Pyle RL, van Mierop LHS, et al. Hereditary defects of the conotruncal septum in Keeshond dogs: pathologic and genetic studies. Am J Cardiol 34:187, 1974
90. Ringwald RE, Bonagura JD. Tetralogy of Fallot in the dog: clinical findings in 13 cases. J Am Anim Hosp Assoc 24:33, 1988
91. Patterson DF, Pyle RL, van Mierop LHS, et al. Hereditary defects of the conotruncal septum in keeshond dogs: pathologic and genetic studies. Am J Cardiol 34:187, 1974
92. Eyster GE, Weber W, McQuillan W. Tetralogy of Fallot in a cat. J Am Vet Med Assoc 171:280, 1977
93. van Heerden J, Lourens DC. Tetralogy of Fallot in a two-and-one half-year-old cat. J Am Anim Hosp Assoc 17:129, 1981
94. Hawe RS, Witter WR, Wilson JB. Tetralogy of Fallot in a five-year-old cat. J Am Anim Hosp Assoc 15:329, 1979
95. Lombard CE, Twitchell MJ. Tetralogy of Fallot, persistent left cranial vena cava, and retinal detachment in a cat. J Am Anim Hosp Assoc 14:624, 1978
96. Helphry ML. Vascular ring anomalies in the dog. Vet Clin North Am 9:207, 1979
97. Van den Ingh TSDAM, van der Linde-Sipman JS. Vascular rings in the dog. J Am Vet Med Assoc 164:939, 1974
98. Ellison GW. Vascular ring anomalies in the dog and cat. Comp Contin Educ 11:693, 1980
99. Ettinger SJ, Suter PF. Canine Cardiology. Philadelphia, WB Saunders, 1970
100. Shires PK, Liu SK. Persistent right aortic arch in dogs: a long-term follow-up after surgical correction. J Am Anim Hosp Assoc 17:773, 1981
101. Aultman SH, Chambers JN, Vestre WA. Double aortic arch and persistent right aortic arch in two litter mates: surgical treatment. J Am Anim Hosp Assoc 16:533, 1980
102. Wheaton LG, Blevins WE, Weirich WE. Persistent right aortic arch associated with other vascular anomalies in two cats. J Am Vet Med Assoc 184:848, 1984
103. Martin DG, Ferguson EW. Double aortic arch in a dog. J Am Vet Med Assoc 183:967, 1983
104. Hurley K, Miller MW, Willard MD, et al. Left aortic arch and right ligamentum arteriosum causing esophageal obstruction in a dog. J Am Vet Med Assoc 203:410, 1993
105. Eyster GE, Carring CB, Baker B, et al. Coarctation of the aorta in a dog. J Am Vet Med Assoc 169:426, 1976
106. Nichols JB, Eyster GE, Dulisch ML, et al. Aortic interruption in a dog. J Am Vet Med Assoc 174:1091, 1979
107. Nelson AW. Aorticopulmonary window in a dog. J Am Vet Med Assoc 188:1055, 1986
108. Will JW. Subvalvular pulmonary stenosis and aorticopulmonary septal defect in the cat. J Am Vet Med Assoc 154:913, 1969
109. Buchanan JW. Persistent cranial left vena cava in dogs: angiocardiography, significance, and coexisting anomalies. J Am Vet Rad Soc 4:1, 1963
110. Hilwig RL, Bishop SP. Anomalous pulmonary venous return in a Great Dane. Am J Vet Res 36:299, 1975
111. Hosgood G. Arteriovenous fistulas: pathophysiology, diagnosis, and treatment. Comp Cont Ed 11:5, 1989
112. Suter PF, Fox PR. Peripheral vascular disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed, Vol I. Philadelphia, WB Saunders, 1995, p 1068
113. Rutgers HC, Batt RM, Haywood S. Hepatic organelle pathology in dogs with congenital portosystemic shunts. J Vet Intern Med 5:351, 1991
114. Birchard SJ. Feline portacaval shunts. Compend Small Anim Med Pract Vet 14:1295, 1992
115. Liu SK. Pathology of feline heart diseases. *In* Kirk R (ed). Current Veterinary Therapy. Vol V, Philadelphia, WB Saunders, 1974, p 341
116. Scott FW, Weiss RC, Post JE, et al. Kitten mortality complex (neonatal FIP?). Feline Pract 9:44, 1979
117. Bryan CS, Oppenheimer EH. Ventricular endocardial fibroelastosis: basis for its presence or absence in cases of pulmonic and aortic atresia. Arch Pathol Lab Med 87:82, 1969
118. Paaseh LH, Zook BC. The pathogenesis of endocardial fibroelastosis in the Burmese cat. Lab Invest 42:197, 1980
119. Moller JH, Lucas RV, Adams P, et al. Endocardial fibroelastosis: a clinical and anatomic study of 47 patients with emphasis on its relationship to mitral insufficiency. Circulation 30:759, 1964
120. Liu SK, Tilley LP. Malformations of the canine mitral valve complex. J Am Vet Med Assoc 167:465, 1975
121. Roberts WC, Morrow AG. Secondary left ventricular endocardial fibroelastosis following mitral valve replacement—cause of cardiac failure in late postoperative period. Circulation 37(suppl II): 101, 1968

121a. Ni J, Bowles N, Kim Y, et al. Viral infection of the myocardium in endocardial fibroelastosis. Molecular evidence for the role of mumps virus as an etiologic agent. Circulation 95:133, 1997
122. Liu SK, Fox PR, Tilley LP. Excessive moderator bands in the left ventricle of 21 cats. J Am Vet Med Assoc 180:1215, 1982
123. Keene BW, Bonagura JD. Valvular heart disease. *In* Kirk RW (ed). Current Veterinary Therapy. Vol VIII. WB Saunders, Philadelphia, 1983, p 311
124. Zook BC. Some spontaneous cardiovascular lesions in dogs and cats. Comparative pathology of the heart. Adv Cardiol 13:148, 1974
125. Jones TC, Zook BC. Aging changes in the vascular system of animals. Ann NY Acad Sci 127:671, 1965
125a. Buchanan JW. Valvular disease (endocardiosis in dogs). Adv Vet Sci Comp Med 21:75, 1079
126. Das KM, Tashjian RJ. Chronic mitral valve disease in the dog. Vet Med 60:1209, 1965
127. Detweiler DK, Luginbuhl H, Buchanan JW, et al. The natural history of acquired cardiac disability in the dog. Ann NY Acad Sci 147:318, 1968
128. Buchanan JW. Chronic valvular disease (endocardiosis) in dogs. Adv Vet Sci Comp Med 21:75, 1977
129. Whitney JC. Cardiovascular pathology. J Small Anim Pract 8:459, 1967
130. Fenoglio JJ, Tuan DP, Wit AL, et al. Canine mitral complex. Circ Res 31:417, 1972
131. Chakrabarti B, Park JW. Glycosaminoglycans: structure and interaction. CRC Rev Biochem 8:225, 1980
132. King BD, Clark MA, Baba N, et al. "Myxomatous" mitral valve: collagen dissolution as the primary defect. Circulation 66:288, 1982
133. Calvert CA. Endocarditis and bacteremia. *In* Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 419
134. Calvert CA. Valvular bacterial endocarditis in the dog. J Am Vet Med Assoc 180:1080, 1982
135. Anderson CA, Dubielzig RR. Vegetative endocarditis in dogs. J Am Anim Hosp Assoc 20:149, 1984
136. Murdoch DB, Baker JR. Bacterial endocarditis in the dog. J Small Anim Pract 18:687, 1977
137. Sisson D, Thomas WP. Endocarditis of the aortic valve in the dog. J Am Vet Med Assoc 184:570, 1984
138. Fox PR, Nichols CER. Cardiac involvement in systemic disease. *In* Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 565
139. Yamaguchi RA, Pipers FA, Gamble DA. Echocardiographic evaluation of a cat with bacterial vegetative endocarditis. J Am Vet Med Assoc 183:118, 1983
140. Muna WFT, Ferrans VJ, Pierce JE, et al. Discrete subaortic stenosis in Newfoundland dogs: association of infective endocarditis. Am J Cardiol 41:746, 1978
141. Van Vleet JF, Ferrans VJ. Myocardial diseases of animals. Am J Pathol 124:98, 1986
142. Fox PR. Feline myocardial diseases. *In* Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 467
143. Sisson DD, Thomas WP. Myocardial diseases. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed, Vol I. Philadelphia, WB Saunders, 1995, p 995
144. Tilley LP, Liu SK, Gilbertson SR, et al. Primary myocardial disease in the cat. A model for human cardiomyopathy. Am J Pathol 87:493, 1977
145. Liu SK, Maron BJ, Tilley LP. Feline hypertrophic cardiomyopathy: gross anatomic and quantitative histologic features. Am J Pathol 102:388, 1981
146. Liu SK, Maron BJ, Tilley LP. Hypertrophic cardiomyopathy in the dog. Am J Pathol 84:497, 1979
147. Sisson DD. Heritability of idiopathic myocardial hypertrophy and dynamic subaortic stenosis in pointer dogs (Abstract). J Vet Intern Med 4:118, 1990
147a. Thomas WP, Mathewson JW, Suter PF, et al. Hypertrophic obstructive cardiomyopathy in a dog: clinical, hemodynamic, angiographic and pathologic studies. J Am Hosp Assoc 20:253, 1984
148. Liu SK, Peterson ME, Fox PR. Hypertrophic cardiomyopathy and hyperthyroidism in the cat. J Am Vet Med Assoc 185:52, 1984
148a. Kushwaha SS, Fallon JT, Furster V. Medical progress: restrictive cardiomyopathy. N Engl J Med 336:267, 1997
149. Littman MP. Spontaneous systemic hypertension in 24 cats. J Vet Intern Med 8:79, 1994
150. Lesser M, Fox PR, Bond BR. Assessment of hypertension in 40 cats with left ventricular hypertrophy by Doppler-shift sphygmomanometry. J Small Anim Pract 33:55, 1992
151. Fox PR, Broussard JD, Peterson ME. Electrocardiographic and radiographic changes in cats with hyperthyroidism: 1979–1982 vs 1992. J Am Anim Hosp Assoc (in press)
151a. Kittleson ME, Pion PD, DeLellis LA, et al. Increased serum growth hormone concentration in feline hypertrophic cardiomyopathy. J Vet Intern Med 6:320, 1992
152. Factor SM, Sonnenblick EH. Pathogenesis of clinical and experimental cardiomyopathies: recent concepts. Prog Cardiovasc Dis 27:359, 1985
153. Pion PD, Kittleson MD, Rogers QR, et al. Myocardial failure in cats associated with low plasma taurine: a reversible cardiomyopathy. Science 237:764, 1987
154. Fox PR. Feline myocardial disease. 18th Annual Waltham/OSU Symposium. Vernon, CA, Waltham, USA, 1994, p 119
154a. Fox PR, Petnie JP, Liu SK, et al. Clinical and pathologic features of cardiomyopathy characterized by myocardial failure in 49 cats: 1990–1995 (Abstr). J Vet Int Med 11:139, 1997
154b. Tidholm A, Häggström J, Jönsson L. Prevalence of attenuated wavy fibers in myocardium of dogs with dilated cardiomyopathy. J Am Vet Med Assoc 212:1732, 1998
155. Fuster VF, Gersh BJ, Guiliani ER, et al. The natural history of idiopathic dilated cardiomyopathies. Am J Cardiol 47:525, 1981
156. Keene BW. L-Carnitine deficiency in canine dilated cardiomyopathy. *In* Kirk RW, Bonagura JD (eds). Kirk's Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1992, p 780
156a. Kramer GA, Kittleson MD, Fox PR, et al. Plasma taurine concentrations in normal dogs and dogs with heart disease. J Vet Intern Med 9:253, 1995
156b. Kittleson MD, Keene B, Pion PD, et al. Results of the multicenter spaniel trial (MUST): taurine- and carnitine-responsive dilated cardiomyopathy in American cocker spaniels with decreased plasma taurine concentration. J Vet Int Med 11:204, 1997
157. Harpster NK: Boxer cardiomyopathy. *In* Kirk RW (ed). Current Veterinary Therapy. Vol VIII. Philadelphia, WB Saunders, 1983, p 329
158. Harpster NK. Boxer cardiomyopathy. A review of the long-term benefits of antiarrhythmic therapy. Vet Clin North Am: Small Anim Pract 21:989, 1991
159. Fox PR. Restrictive cardiomyopathy. Proceedings, 14 Annual Veterinary Medicine Forum, 1996, p 235
160. Bonagura JD, Fox PR. Restrictive cardiomyopathy. *In*

Bonagura JD (ed). Kirk's Current Veterinary Therapy. Vol XII. Philadelphia, WB Saunders, 1995, p 863
161. Benotti JR, Grossman W, Wohn PF. Clinical profile of restrictive cardiomyopathy. Circulation 61:1206, 1980
162. Wynne J, Braunwald E. The cardiomyopathies and myocarditides. *In* Braunwald E (ed). Heart Disease. A Textbook of Cardiovascular Medicine. 5th ed, Vol 2. Philadelphia, WB Saunders, 1997, p 1404
163. Olsen EGJ, Spry CJF. The pathogenesis of Löffler's endomyocardial disease, and its relationship to endomyocardial fibrosis. *In* Yu PN, Goodwin JF (eds). Progress in Cardiology. Vol 8. Philadelphia, Lea & Febiger, 1979, p 281
164. Levine RA. Echocardiographic assessment of the cardiomyopathies. *In* Weyman AE (ed). Principles and Practice of Echocardiography. 2nd ed. Philadelphia, Lea & Febiger, 1994, p 781
165. Bossbally MJ, Stalis I, Knight D, et al. Feline endomyocarditis: a clinical/pathological study of 44 cases (Abstract). J Vet Intern Med 8:144, 1994
166. Stalis IH, Bossbally MJ, Van Winkle TJ. Feline endomyocarditis and left ventricular endocardial fibrosis. Vet Pathol 32:122, 1995
167. Liu SK, Tilley LP. Animal models of primary myocardial disease. Yale J Biol Med 53:191, 1980
168. Truex RC, Warshow LJ. The incidence and size of the moderator band in man and in mammals. Anat Rec 82:361, 1941
168a. Valentine BA. Development of Duchenne-type cardiomyopathy: morphologic studies in a canine model. Am J Pathol 135:671, 1989
168b. Valentine BA. Canine X-linked muscular dystrophy as an animal model of Duchenne muscular dystrophy: a review. Am J Med Genet 42:353, 1992
168c. Moïse NS. Duchenne's cardiomyopathy in a canine model: electrocardiographic and echocardiographic studies. Am J Cardiol 17:812, 1991
169. Miller ME, Christensen GC, Evans HE. Anatomy of the Dog. 2nd ed. Philadelphia, WB Saunders, 1964
170. Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis: a histopathologic definition and classification. Am J Cardiovasc Pathol 1:3, 1987
171. Atkins CE. The role of noncardiac disease in the development and precipitation of heart failure. Vet Clin North Am 21:1023, 1991
172. Liu SK. Myocarditis and cardiomyopathy in the dog and cat. *In* Sekiguchi M, Olsen EGJ, Goodwin JF (eds). Myocarditis and Related Disorders. Tokyo, Springer-Verlag, 1985, p 122
173. Carpenter JL, Roberts RM, Harpster NK, King NW. Intestinal and cardiopulmonary forms of parvovirus infection in a litter of pups. J Am Vet Med Assoc 176:1269, 1980
174. Meunier PC, Cooper BJ, Appel MJG, et al. Experimental viral myocarditis: parvoviral infection of neonatal pups. Vet Pathol 21:509, 1984
175. Liu SK, Keene BW, Fox PR. Myocarditis in the dog and cat. *In* Bonagura JD (ed). Kirk's Current Veterinary Therapy. Vol XII. Philadelphia, WB Saunders, 1995, p 842
176. Liu SK. Myocarditis and cardiomyopathy in the dog and cat. Heart Vessels 1:122, 1985
176a. Meurs KM, Fox PR, Magnon A, et al. Polymerase chain reaction (PCR) analysis for feline viruses in formalin-fixed cardiomyopathic hearts identifies panleukopenia (Abstr). J Vet Int Med 12:201, 1998
177. Eisenstein BI. The polymerase chain reaction: a new method of using molecular genetics for medical diagnosis. N Engl J Med 322:178, 1990
178. Barr SC, Schmidt SP, Brown CC, et al. Pathologic features of dogs inoculated with North American *Trypanosoma cruzi* isolates. Am J Vet Res 52:2033, 1991
179. Hirsch J. Hypercoagulability. Semin Hematol 14:409, 1977
180. Furster V, Chesebro JH. Antithrombotic therapy: role of platelet-inhibitor drugs. I. Current concepts of thrombogenesis: role of platelets. Mayo Clin Proc 56:102, 1981
181. Griffiths I, Duncan ID. Ischaemic neuromyopathy in cats. Vet Rec 104:518, 1979
182. Suter PF, Fox PR. Peripheral vascular disease. *In* Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine. 4th ed, Vol 1. Philadelphia, WB Saunders, 1995, p 1068
183. Green RA, Russo EA, Greene RT, et al. Hypoalbuminemia-related platelet hypersensitivity in two dogs with nephrotic syndrome. J Am Vet Med Assoc 186:485, 1985
184. De Bartola SP, Meuten DJ. Renal amyloidosis in two dogs presented for thromboembolic phenomena. J Am Anim Hosp Assoc 16:129, 1980
185. Burns MG, Kelly AB, Hornof WJ, et al. Pulmonary artery thrombosis in three dogs with hyperadrenocorticism. J Am Vet Med Assoc 178:388, 1981
186. LaRue MI, Murtaugh RJ. Pulmonary thromboembolism in dogs: 47 cases (1986–1987). J Am Vet Med Assoc 197:1368, 1990
187. Fluckiger MA, Gomez JA. Radiographic findings in dogs with spontaneous pulmonary thromboembolism or embolism. Vet Radiol 25:124, 1984
188. Klein MK, Dow SW, Rosychuck RAWI. Pulmonary thromboembolism associated with immune-mediated anemia in dogs: ten cases (1982–1987). J Am Vet Med Assoc 195:246, 1989
189. Baty CJ, Hardie EM. Pulmonary thromboembolism: diagnosis and treatment. *In* Kirk RW, Bonagura JD (eds). Kirk's Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1992, p 137
190. Schaub RG, Rawlings CA. Pulmonary vascular response during phases of canine heartworm disease: a scanning electron microscopic study. Am J Vet Res 41:1082, 1980
191. Schaub RG, Rawlings CA, Keith JC. Platelet adhesion and myointimal proliferation in canine pulmonary arteries. Am J Pathol 104:13, 1981
192. Keith JC, Schaub RG, Rawlings CA. Early arterial injury-induced myointimal proliferation in canine pulmonary arteries. Vet Res 44:181, 1983
193. Rawlings CA, Losonsky JM, Schaub RG. Post-adulticide changes in *Dirofilaria immitis*-infected beagles. Am J Vet Res 44:8, 1983
194. Rawlings CA, Losonsly JM, Lewis RE. Development and resolution of radiographic lesions in canine heartworm disease. J Am Vet Med Assoc 178:1172, 1981
195. Bellah JR, Whitton DL, Ellison GW, et al. Surgical correction of concomitant cranioventral abdominal wall, caudal sternal, diaphragmatic, and pericardial defects in young dogs. J Am Vet Med Assoc 195:1722, 1989
196. Sisson D, Thomas WP, Reed J, et al. Intrapericardial cysts in the dog. J Vet Intern Med 7:364, 1993
197. Reed JR. Pericardial diseases. *In* Fox PR (ed). Canine and Feline Cardiology. New York, Churchill Livingstone, 1988, p 495
198. Sisson DD, Thomas WP, Ruehl WW, et al. Diagnostic value of pericardial fluid analysis in the dog. J Am Vet Med Assoc 184:51, 1984
199. Miller MW, Fossum TW. Pericardial disease. *In* Kirk RW, Bonagura JD (eds). Kirk's Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1992, p 725

200. Rush JE, Keene BW, Fox PR. Pericardial disease in the cat: a retrospective evaluation of 66 cases. J Am Anim Hosp Assoc 26:39, 1990
201. McDonough SP, MacLachlan NJ, Tobias AH. Canine pericardial mesothelioma. Vet Pathol 29:256, 1992
202. Liu SK. Acquired cardiac lesions leading to congestive heart failure in the cat. J Am Vet Med Assoc 31:2071, 1970
203. Meierhenry EF, Liu SK. Atrioventricular bundle degeneration associated with sudden death in the dog. J Am Vet Med Assoc 172:1418, 1978
204. James TN, Robertson BT, Malds AL, et al. Hereditary stenosis of the His bundle in the Pug dog. Circulation 52:1152, 1975
204a. Sandusky GE, Kerr CM, Capen CC. Morphologic variations and aging in the atrioventricular conduction system of large breed dogs. Anat Rec 193:883, 1979
205. Tilley LP, Liu SK. Persistent atrial standstill in the dog and cat (Abstract). Sci Proc Am Coll Vet Intern Med, 1983, p 43
205a. Miller MS, Tilley LP, Atkins CE. Persistent atrial standstill (atrioventricular muscular dystrophy). *In* Kirk RW, Bonagura JD (eds). Kirk's Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1992, p 786
206. Bloomfield MB, Sinclair-Smith BC. Persistent atrial standstill. Am J Med 39:335, 1965
206a. Mostafa IA. A case of glycogenic cardiomegaly in a dog. Acta Vet Scand 11:197, 1970
206b. Walvoort HC, van Ness JJ, Stockhof AA, et al. Canine glycogen storage disease type II. A clinical study of four affected Lapland dogs. J Anim Hosp Assoc 20:279, 1984
207. Jönsson L. Coronary arterial lesion and myocardial infarcts in the dog. A pathologic and microrangiographic study. Acta Vet Scand (Suppl 38) 13:1, 1972
208. Luginbühl H, Detweiler DK. Cardiovascular lesions in dogs. Ann NY Acad Sci 127:517, 1965
209. Luginbühl H, Jones JET, Detweiler DK. The morphology of spontaneous arteriosclerotic lesions in the dog. *In* Roberts JC Jr, Straus R (eds). Comparative Arteriosclerosis. New York, Harper & Row, 1965, p 161
210. Lindsay S, Chaikoff IL, Gilmore JW. Arteriosclerosis in the dog. 1. Spontaneous lesions in the aorta and coronary arteries. Arch Pathol 53:281, 1952
210a. Callanan JJ, Jones BA, Willett BJ, et al. Histologic classification and immunophenotype of lymphosarcomas in cats with naturally and experimentally acquired feline immunodeficiency virus infections. Vet Pathol 33:264, 1996
211. Kelly DF, Gaskell CJ, Lee MA. Arteriosclerosis of coronary arteries in Labradors with congestive heart failure. J Small Anim Pract 33:437, 1992
212. Robinson M. Generalized atherosclerosis in a dog. J Small Anim Pract 17:45, 1976
213. Liu SK, Hsu FS, Lee RCT. An Atlas of Cardiovascular Pathology. Taiwan, Republic of China, Pig Research Institute, Wonder Enterprises Co Ltd and Shin Chaan Color Printing Inc, 1989
214. Liu SK, Tilley LP, Tappe JP, Fox PR. Clinical and pathologic finds in dogs with atherosclerosis: 21 cases (1970–1983). J Am Vet Med Assoc 189:227, 1986
215. Liu SK. Myocardial infarction in animals. Proceedings, 2nd International Symposium on the Pig Model for Biomedical Research, Miaoli. Taiwan, Republic of China, Pig Research Institute, 1992, p 205
216. Detweiler DK. Spontaneous and induced arterial disease in the dog: pathology and pathogenesis. Toxicol Pathol 17 (Part 2):94, 1989
217. Lucke VM. Renal disease in the domestic cat. J Pathol Bacteriol 95:67, 1968
218. Mohr FC, Carpenter JL. Arteriosclerosis in a cat. Vet Pathol 24:466, 1987
219. Lefbom BK, Adams WH, Weddle DL. Mineralized arteriosclerosis in a cat. Vet Radiol Ultrasound 37:420, 1996
220. Liu SK, Fox PR. Myocardial ischemia and infarction. *In* Kirk RW, Bonagura JD (eds). Kirk's Current Veterinary Therapy. Vol XI. Philadelphia, WB Saunders, 1992, p 791
221. Guarda F, Bussadori C, Scotti C, et al. Correlazioni anatomo-cliniche nella cardiopatia ischemica del cane. Veterinaria 3:5, 1989
221a. DeFrancesco TC, Atkins CE, Keene BW. Myocardial infarction complicating management of congestive heart failure in a dog. J Am Anim Hosp Assoc 32:68, 1996
222. Sandersleben JV. Der Infarkt und seine Bedeutung beim Haustier. Tierärztl Wschr 68:590, 1961
223. Nielsen SW, Nielsen LB. Coronary embolism in valvular bacterial endocarditis in two dogs. J Am Vet Med Assoc 125:376, 1954
224. Hamlin RL. Prognostic value of changes in the cardiac silhouette in dogs with mitral insufficiency. J Am Vet Med Assoc 153:1436, 1968
225. Scholz DG, Kitzman DW, Hagen PT, et al. Age-related changes in normal human hearts during the first 10 decades of life. Part I (growth): A quantitative anatomic study of 200 specimens from subjects from birth to 19 years old. Mayo Clin Proc 63:126, 1988
226. Scholz DG, Kitzman DW, Hagen PT, et al. Age-related changes in normal human hearts during the first 10 decades of life. Part II (maturity): A quantitative anatomic study of 765 specimens from subjects 20 to 99 years old. Mayo Clin Proc 63:137, 1988
227. Pearson AC, Gudipati CV, Labovitz AJ. Effects of aging on left ventricular structure and function. Am Heart J 121:871, 1991
228. Wei JY. Age and the cardiovascular system. N Engl J Med 327:1735, 1992
229. White M, Roden R, Minobe W, et al. Age-related changes in β-adrenergic neuroeffector systems in the human heart. Circulation 90:1225, 1994

37

Necropsy Techniques for the Heart and Great Vessels

SANFORD P. BISHOP

OBJECTIVES FOR THE NECROPSY EXAMINATION

The major goal of necropsy is to record gross anatomic abnormalities and determine the cause of death. Specialized methods for specific anatomic, immunohistochemical, and electron microscopic examination are sometimes employed. Postmortem methods should be guided by a thorough review of the clinical history and data base and have been developed for examination of the cardiovascular system.[1–6]

NECROPSY PROCEDURES

EXTERNAL EXAMINATION

A thorough external examination is first conducted. Body weight and general body condition are recorded. Particular attention is given to any abnormal fluid accumulations that will affect measured ratios of heart or chamber weight to body weight.[7] The left thoracic cavity is opened by cutting the ribs at the sternal border near their vertebral connection, and reflecting the rib cage dorsally. Thoracic arteries and veins are dissected *in situ* and examined for abnormalities. For example, attention is directed to the ligamentum arteriosus (possible patent ductus arteriosus); vessels originating from the aortic arch (aberrant origin of left subclavian artery); location of the venae cavae and azygos vein (persistent left anterior vena cava); the presence of thrombi or masses; the general relationship of the heart and great vessels; and any adhesions.

EXTRACTING THORACIC ORGANS

The heart and lungs are then removed *en bloc* from the thorax, including

the entire trachea and larynx, transecting the large vessels at the thoracic inlet and diaphragm. The pericardium should be opened, noting any fluid accumulation, and the lungs removed by transecting the pulmonary artery and veins 1 to 3 cm from their origin. The aorta and venae cavae are transected 1 to 3 cm from the heart. The external cardiac surface is examined for fibrin tags, scars, or other abnormalities.

OPENING THE HEART

RIGHT ATRIUM AND VENTRICLE

Next, the heart is opened by an initial incision into the main pulmonary artery. This is then extended into the right ventricle along the junction of the right ventricular free wall and the interventricular septum, downward to the cardiac apex following the septal wall, and finally up the posterior heart border into the right atrium (RA). In the RA, the incision is made approximately 1 cm dorsal and parallel to the coronary groove into the right auricle. The cranial vena cava is not incised, since this would destroy the sinoatrial node for histologic examination (Fig. 37–1*A,B*).

LEFT ATRIUM AND VENTRICLE

By inserting a blade into one of the pulmonary veins and extending the incision into the left auricle, the left atrium (LA) is opened. The endocardial surface of the LA is examined for focal endocardial thickening, jet lesions, or endocardial tears indicative of mitral valve insufficiency,[7] or for thrombi in cats.[8] Mitral valve leaflets are carefully inspected from the left atrium before incising the mitral annulus, taking careful note of the valve surface and the chordae tendineae for thickening, vegetations, or rupture.

An incision is then made down the left ventricular posterior wall between the posterior papillary muscle of the left ventricle (LV) and the interventricular septum (it is necessary to cut some of the chordae tendineae of the mitral valve). If it is desired not to cut these chordae tendineae, the incision should be made directly through the middle of the posterior papillary muscle. In this fashion the LV is opened with an incision from the LA to the left ventricular apex, bisecting the posterior papillary muscle. The LV incision is then continued from the apex toward the base, along the anterior wall of the heart and into the LV outflow tract to the aorta (Fig. 37–1*C,D*). In the cat, care should be taken to avoid inadvertent cutting of abnormal left ventricular moderator bands, if present, which may bridge the left ventricular septum and free wall.[9] Ultimately, these may need to be severed to permit reflection of the left ventricular wall. The heart is now completely opened, and all the valvular complexes and endocardium may be examined.

NECROPSY MEASUREMENTS

ATRIOVENTRICULAR ANNULUS

Using a flexible ruler or a piece of string, the opened left and right atrioventricular (AV) valve rings

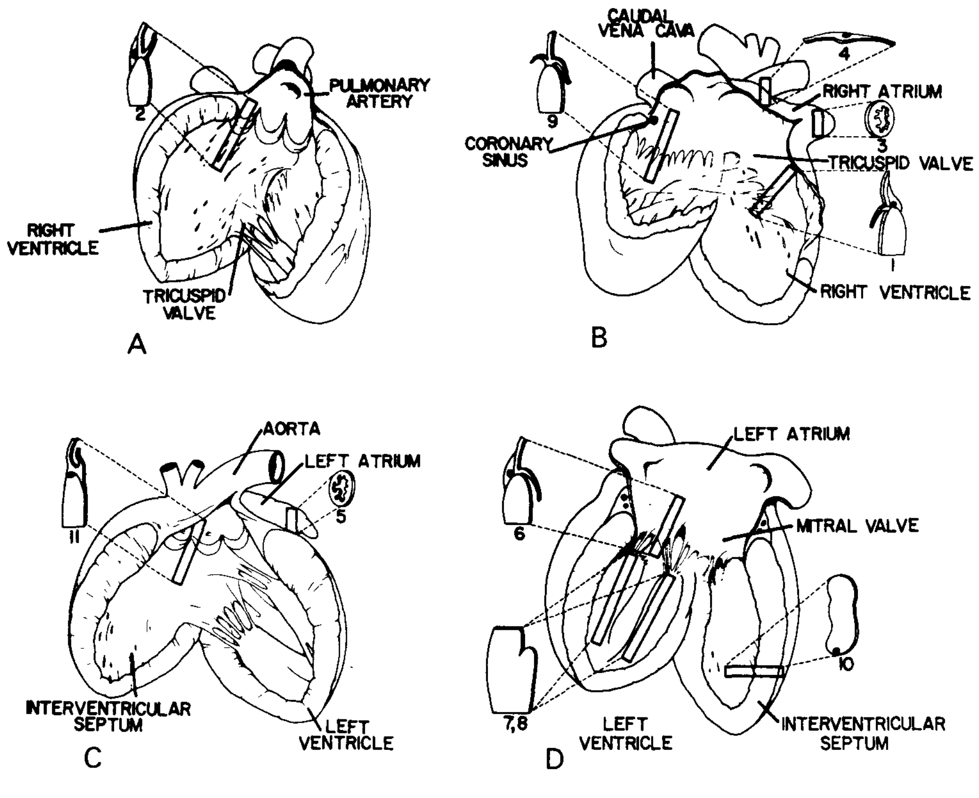


FIGURE 37–1

Diagram of heart opened along lines of blood flow as described in text. Numbered drawings illustrate the shape and location of tissues removed for histologic section. (A) Right ventricular cavity, right ventricular outflow tract, and pulmonary artery. (B) Right ventricle and right atrium. (C) Left ventricle, left ventricular outflow tract, and aorta. (D) Left ventricle and left atrium.

TABLE 37–1
Heart Weight, Body Weight, and Associated Ratios in Normal Dogs and Cats

		BW (kg)	HW/BW (g/kg)	RV/BW (g/kg)	LV+S/BW (g/kg)	RV/HW (g/kg)	LV+S/HW (g/kg)	LV+S/RV (g/kg)
Normal	(mean)	10.22	6.69	1.37	4.25	0.207	0.650	3.13
Beagle (n = 26)	(SD)	1.23	0.68	0.17	0.42	0.014	0.034	0.23
Normal	(mean)	13.49	7.41	1.67	4.71	0.225	0.635	2.82
Mixed-breed dogs (n = 47)	(SD)	5.18	1.02	0.26	0.67	0.2	0.028	0.23
Normal	(mean)	3.08	3.68	0.67	2.41	0.184	0.659	3.56
Cats (n = 33)	(SD)	0.57	0.60	0.15	0.37	0.025	0.025	0.23

BW, body weight; HW, total heart weight; LV+S, left ventricle plus septum; RV, right ventricular free wall; SD, standard deviation.

should be measured. These are expressed as a ratio of left-to-right AV ring circumference. The normal ratio for the dog (mean ± standard deviation) is 0.90 ± 0.07; for the cat, 0.82 ± 0.07. Deviations from this ratio are useful indicators of AV ring dilation.

HEART WEIGHT RATIOS

The heart is weighed after completely trimming extraneous tissue at the base. The ratio of heart weight to total body weight is used to assess cardiac or specific heart chamber mass and hypertrophy between animals or to a normal set of values (Tables 37–1, 37–2). To quantify the degree of left or right ventricular hypertrophy or atrial enlargement, weights of the combined atria, right ventricular free wall, and the combined LV and interventricular septum should be obtained. The dissection is made by completing the separation of the right ventricular free wall from the RA at the coronary groove, continuing through the crista supraventricularis to the pulmonic valve. The LA is separated completely from the LV at the AV ring. The RV free wall weight and combined LV and interventricular septal weight are obtained.

One must be careful to avoid spurious changes in total body weight resulting from disease or therapy. For example, morbid obesity, severe ascites, or other effusions will cause the heart weight to body weight ratio to become lower than normal; conversely, severe loss of body weight as in chronic cachexia may cause a greater than normal heart weight to body weight ratio. Normal total cardiac and regional weight ratios for a group of colony-raised beagles, a group of mixed-breed dogs, and normal adult cats are given (Table 37–1). Heart weight to body weight ratios in various feline myocardial diseases and for another group of normal cats are also listed (Table 37–2).[10] The use of a measurement not affected by body condition, such as tibial length or brain weight, has been utilized by some investigators to normalize cardiac weights, thus avoiding the problem of changes in body condition.

WALL THICKNESS

Measurement of wall thickness of the ventricles is markedly affected by the stage of rigor mortis, which is influenced by terminal disease conditions, time after death, and temperature. Thus, postmortem changes may alter wall thickness, resulting in values considerably different from premortem values. Generally, LV wall thickness at necropsy exceeds that recorded by echocardiography during life.[12]

Wall thickness measurements of the interventricular septum and the left ventricular free wall are useful to assess various forms of hypertrophic cardiomyopathy.[10–13] To make this measurement, an incision is made from base to apex, perpendicular to the endocardial and epicardial surfaces, through the interventricular septum below the aortic valves and the LV free wall between the papillary muscles. Wall thickness is mea-

TABLE 37–2
Heart Weight, Body Weight, and Associated Ratios in Normal and Cardiomyopathic Cats

Myocardial Disease	Number	Body Weight (kg)	Heart Weight (g)	Heart Wt/Body Wt (g/kg)
Hyperthyroid	23	3.3 ± 0.3	22.6 ± 2.1	7.0 ± 0.3
Restrictive	15	4.5 ± 0.2	30.6 ± 1.7	6.4 ± 0.3
Symmetric hypertrophic	35	4.5 ± 0.2	27.5 ± 0.8	6.3 ± 0.1
Asymmetric hypertrophic	16	4.4 ± 0.1	27.5 ± 0.8	6.3 ± 0.3
Dilated (congestive)	21	4.5 ± 0.1	24.1 ± 0.9	5.4 ± 0.3
Excessive moderator band	21	4.5 ± 0.2	21.6 ± 0.8	4.5 ± 0.2
Control (normal)	36	4.8 ± 0.2	18.4 ± 0.6	3.83 ± 0.2

Values are mean ± SEM.
From Liu SK, Peterson ME, Fox PR: Hypertrophic cardiomyopathy and hyperthyroidism in the cat. J Am Vet Med Assoc 185:52, 1984.

sured at the thickest point in each wall, usually about one fourth the distance from the base to the apex, avoiding papillary or trabecular muscles. Normal ratios of interventricular septum/LV free wall thickness should not exceed 1.2 to 1.3 in dogs or cats.[1, 10–13] Ratios greater than these values indicate asymmetric septal hypertrophy.

Measurement of chamber diameter is difficult and imprecise in the unfixed opened heart. Nevertheless, a subjective evaluation of the degree of chamber dilation or hypertrophy is made by inspecting the general chamber shape, and the size of the papillary muscles. Papillary muscles assume a smaller, more flattened form in dilated hearts and a more thickened, prominent form with hypertrophy.

HISTOPATHOLOGIC EVALUATION OF THE HEART

Tissue for histopathology should be fixed in 10 percent phosphate-buffered formalin for a minimum of 24 hours. All clotted blood should first be removed by gentle washing in fixative. Histopathologic sections should be taken as blocks of tissue less than 3 mm thick. The location and shape of tissue blocks, which should include all major anatomic regions of the heart, is illustrated in Figure 37–1. To aid in histopathologic evaluation, a hematoxylin and eosin stain, a trichrome stain (for fibrosis), and an elastin stain are recommended. The Gomori aldehyde fuchsin stain with a Gomori trichrome counterstain is useful to identify collagen and elastic tissue.

SPECIAL FIXATION PROCEDURES

The choice of fixative depends on the studies to be performed. For light microscopy, 10 percent phosphate-buffered formalin is appropriate. Electron microscopy requires glutaraldehyde or paraformaldehyde fixation. A 2 percent phosphate- or cacodylate-buffered glutaraldehyde gives ideal fixation for electron microscopy but renders the tissue somewhat brittle, causing difficulty in sectioning paraffin-embedded tissue. A combination of 1 percent glutaraldehyde and 1 percent paraformaldehyde (modified Karnofsky fixative) provides a compromise, with excellent fixation and cutting properties for both paraffin- and epoxy-embedded tissues.

IMMERSION FIXATION OF THE ENTIRE HEART

Specialized fixation procedures are required for more precise gross and histopathologic evaluation. Immersion fixation of the entire heart is required if comparison of gross chamber and wall measurements with antemortem imaging tests is desired.[6] Each atrium should first be opened by a single short incision, and the blood removed by flushing with an isotonic solution such as saline. The ventricles and atria are loosely packed with cotton soaked in 10 percent buffered formalin to hold the chamber walls in a shape approximating that *in vivo.* The entire heart is then immersed in 10 percent phosphate-buffered formalin for several days. After fixation, the packing is removed and the heart opened by either transverse or longitudinal cuts. The "breadloaf" method of opening the heart (Fig. 37–2) is useful for examining and measuring wall and chamber dimensions to provide comparison with similar measurements obtained during life. Successive slices from base to apex may be quantitatively measured with computer-assisted digitizer methods to determine ventricular mass, areas of fibrosis, infarct size, chamber dimensions, and wall-to-lumen relationships.[14, 15]

Comparison of the fixed heart with base-apex views obtained by two-dimensional echocardiography is best done by opening the heart longitudinally from base to apex (Fig. 37–3).[6] The fixed heart should be transected through both atria, the LV free wall, interventricular septum, and RV free wall to reveal all walls and chambers. This technique is reliable to compare gross pathologic necropsy changes with antemortem patterns of hypertrophy assessed by two-dimensional echocardiography in cats.[12]

PERFUSION FIXATION

Perfusion fixation of the heart is the preferred method for electron microscopy and is essential for

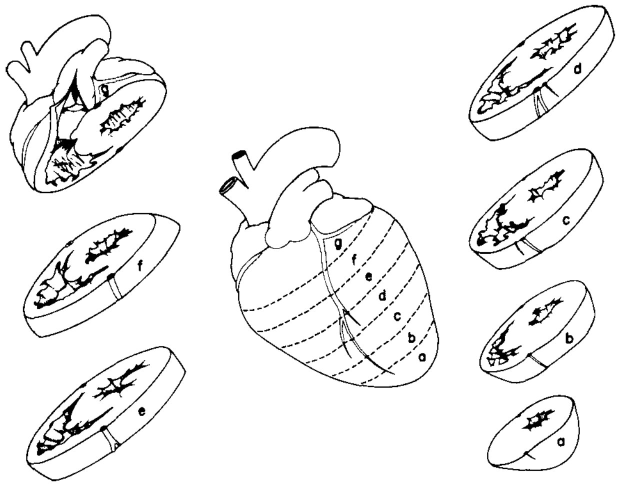


FIGURE 37–2

Diagram illustrating a technique for evaluating the heart using multiple, transverse, cross-sectional slices from apex (slice a) to base (slice g). This is useful for observing distribution of myocardial wall lesions or patterns of ventricular hypertrophy, especially when areas of focal thickening are present.

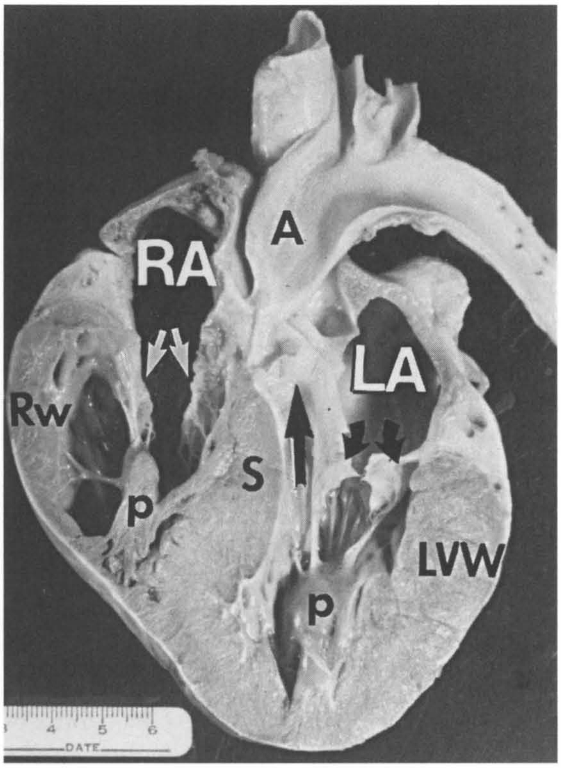


FIGURE 37–3

Canine heart opened according to a transverse base-to-apex orientation. This method of dissection is particularly suitable for comparing the gross heart to tomographic planes accessible with two-dimensional echocardiography, especially the right parasternal long axis view. RA, right atrium; LA, left atrium; S, interventricular septum; LVW, left ventricular free wall; Rw, right ventricular wall; A, ascending aorta; p, papillary muscle. Curved black arrows below the LA point to the mitral valve leaflets and define the left ventricular inflow tract; white arrows below the RA point to tricuspid valve leaflets and define the right ventricular inflow tract; straight black arrow is in the left ventricular outflow tract, and aortic valve cusps lie just distal to the arrow. This dog had documented primary pulmonary hypertension. The right ventricle is enlarged, and hypertrophy of the right ventricular wall is present. (Courtesy of Dr. Philip R. Fox.)

quantitative studies of vascular morphology. Its use is generally reserved for research applications. Due to the elastic nature of blood vessels, severe morphologic distortion results from immersion fixation from vascular contraction. Perfusion fixation is the preferred technique to counteract these potential artifacts.

TECHNIQUE. Perfusion fixation is best accomplished *in situ* under deep anesthesia but can also be done on a freshly extirpated heart. After wide left lateral thoracotomy, loose umbilical tape ligatures are placed around the brachycephalic and subclavian arteries. As large a cannula as will be accommodated is tied retrogradely into the descending thoracic aorta, with the tip in the aortic arch directed toward the heart. The cannula is connected by a Y connector and tubing to two reservoir bottles. One contains a physiologic solution (phosphate-buffered saline) or a suitable cardioplegic solution; the other, a fixative. Alternatively, cannulae may be placed in one or more individual coronary arteries for selective perfusion. Perfusion is performed at a pressure equivalent to *in vivo* diastolic pressure (about 90 mmHg). It is maintained either by gravity, placing the reservoir bottles at the appropriate height, or by a pump with a manometer. The heart is arrested with saturated KCl and the isotonic solution flow started. Simultaneously, aortic branches are ligated to direct all flow to the heart, and the RA or vena cava opened to allow escape of fluid returning from the coronary sinus. Within 2 to 4 minutes, blood will have been washed from the vasculature, and flow is switched to the fixative solution. Flow is continued for 10 to 15 minutes until the heart is uniformly hardened.

REFERENCES

1. Liu SK. Postmortem examination of the heart. Vet Clin North Am 13:379, 1983
2. Layman TE, Edwards JE. A method of dissection of the heart and major pulmonary vessels. Arch Pathol Lab Med 82:314, 1966
3. Coffin DL. Necropsy procedure for the dog and cat. *In* Jones TC, Gleiser CA (eds): Veterinary Necropsy Procedures. Philadelphia, JB Lippincott, 1954
4. Harrison BM. Dissection of the Cat. 5th ed. St. Louis, CV Mosby, 1966
5. Evans HE, deLahunta A. Miller's Guide to the Dissection of the Dog. 2nd ed. Philadelphia, WB Saunders, 1980
6. Edwards WD, Tajik AJ, Seward JB. Standardized nomenclature and anatomic basis for regional tomographic analysis of the heart. Mayo Clin Proc 56:479, 1981
7. Buchanan JW: Chronic valvular disease (endocardiosis) in dogs. Adv Vet Sci Comp Med 21:75, 1977
8. Van Vleet JF, Ferrans VJ, Weirich WE. Pathologic alterations in hypertrophic and congestive cardiomyopathy of cats. Am J Vet Res 41:2037, 1980
9. Liu SK, Fox PR, Tilley LP. Excessive moderator bands in the left ventricles of 21 cats. J Am Vet Med Assoc 180:1215, 1982
10. Liu SK, Peterson ME, Fox PR. Hypertrophic cardiomyopathy and hyperthyroidism in the cat. J Am Vet Med Assoc 185:52, 1984
11. Liu SK, Maron BJ, Tilley LP. Feline hypertrophic cardiomyopathy. Gross anatomic and quantitative histologic features. Am J Pathol 102:388, 1981
12. Fox PR, Liu SK, Maron BJ. Echocardiographic assessment of spontaneously occurring feline hypertrophic cardiomyopathy. An animal model of human disease. Circulation 92:2645, 1995
13. Liu S-K, Maron BJ, Tilley LP. Feline hypertrophic cardiomyopathy. Am J Pathol 1102:388, 1981
14. Ideker RE, Wagner GS, Ruth WK, et al. Evaluation of a QRS scoring system for estimating myocardial infarct size II. Correlation with quantitative anatomic findings for anterior infarcts. Am J Cardiol 49:1604, 1982
15. Ideker RE, Behar VS, Wagner GS, et al. Evaluation of asynergy as an indicator of myocardial fibrosis. Circulation 57:715, 1978

VIII

Cardiovascular Surgery and Procedure

38

Anesthesia and the Heart

DIANE E. MASON

JOHN A. E. HUBBELL

Cardiovascular disease stimulates physiologic and neurohumoral compensatory mechanisms (chapter 11), which can modify myocardial and pulmonary function, result in arrhythmias and circulatory disturbances, and thereby modify the effects of anesthesia. Some animals have only mild heart disease, incidental to the more significant conditions for which anesthesia is required. In other cases, cardiovascular derangement constitutes a major clinical concern complicating anesthetic induction and maintenance, or it poses increased anesthetic risk.

Increasingly, trends in veterinary medicine emphasizing the human-animal bond call for more sophisticated medical and surgical treatment. This often involves anesthetic management of relatively high-risk patients because of congenital or acquired cardiovascular disorders or systemic diseases.

All anesthetic agents either depress cardiovascular function directly or affect reflex cardiovascular mechanisms indirectly. Although routine anesthetic techniques are generally well tolerated by healthy pets, they may potentially destabilize animals with heart disease. No single ideal anesthetic regimen is appropriate for all patients with heart disease; each case must be individually assessed with regard to cardiovascular pathophysiology, coexisting systemic or metabolic diseases, hemodynamic effects of the surgical procedure, influence of anesthesia on the cardiovascular system, and potential interactions between the anesthetics and concurrent medication (Table 38–1).[1, 2]

Prior to anesthetic induction, attention is directed toward cardiovascular assessment and patient stabilization. Selection and administration of appropriate anesthetic drugs require thorough knowledge of their effects on cardiovascular hemodynamics; appropriate patient monitoring, early recognition, and treatment of complications if they arise.

PREOPERATIVE PATIENT ASSESSMENT

The presence of heart disease usually dictates that a more specific and complete preoperative workup than normal be completed.[2a]

HISTORY

A complete and insightful history helps determine the presence of systemic, metabolic, or cardiovascular compromise; the stage of heart failure; and the rate of disease progression. Knowledge of current drug therapy and associated patient response is important. Specific questions should be asked

TABLE 38-1
General Templates and Examples of Sedation, Analgesia, and Anesthesia for Cardiac Patients*

Cardiovascular Disorder	Sedation Only	Analgesia Only	Premedication	Anesthesia		Avoid
				Induction	*Maintenance*	
Dog						
MR (moderate)	A, AOp, Op	B, M, O, Fp	A, AOp, Op	KBen, P, OBen, FBen	I ± Op	X
MR (severe)	A, AOp, Op	B, M, O, Fp	A, AOp, Op	KBen, OBen, FBen	I ± Op	X
DCM	Op, OpBen	B, M, O, Fp	Op, OpBen	KBen, OBen, FBen	I ± Op	A, X
SAS	Op, OpBen	B, M, O, Fp	Op, OpBen	KBen, P, OBen, FBen	I ± Op	A, At, Gy, X
PS	A, AOp, Op	B, M, O, Fp	A, AOp, Op	OBen, FBen, P	I ± Op	
PH	A, AOp, Op	B, M, O, Fp	A, AOp, Op	OBen, FBen, P	I ± Op	X
AF	Op, OpBen	B, M, O, Fp	Op, OpBen	OBen, FBen, P	I ± Op	At, Gy, X
SSS	A, AOp, Op	B, M, O, Fp	A, AOp, Op	KBen, P, OBen, FBen	I ± Op	
PDA	A, AOp, Op	B, M, O, Fp	A, AOp, Op	KBen, P, OBen, FBen	I ± Op	
Cat						
HCM (no failure)	A, AB, AM	B, M, O, Fp	A, AB, AM	KBen, P	I ± M	X
HCM (failure)	B, BBen, M, MBen	B, M, O, Fp	B, BBen, M, MBen	P, I	I ± M	A, X
DCM	B, M, KBen	B, M, O, Fp	B, M, K	KBen, I	I ± M	X
HT	B, BBen, M, MBen	B, M, O, Fp	B, BBen, M, MBen	P, I	I ± M	K, X
SHP	A, ABen, AB, ABBen	B, M, O, Fp	A, ABen, AB, ABBen	P, I	I ± M	K, X

*Drugs separated by a comma (,) indicate that one of these drugs can be selected. Drugs not separated by a comma are to be given together (not necessarily in the same syringe). Check package insert for compatibility.

Drugs

A = Acepromazine (0.01–0.05 mg/kg IM, SC, or IV)
AT = Atropine
B = Butorphanol (0.05–0.2 mg/kg IM, SC, or IV)
Ben = Benzodiazepines, including diazepam (0.05–0.5 mg/kg IV) or midazolam (0.1–0.2 mg/kg IM or IV)
F = Fentanyl (0.01–0.2 mg/kg IV)
Fp = Fentanyl patch
Gy = Glycopyrrolate
I = Isoflurane
K = Ketamine (5–8 mg/kg IV)
M = Morphine (0.5–1.0 mg/kg IM, 2–4 hours) or oxymorphone (0.05–0.1 mg/kg IV, 6–8 hours)
O = Oxymorphone (0.2 mg/kg)
Op = Opioid choice includes butorphanol (0.05–0.2 mg/kg IM, SC, or IV), oxymorphone (0.05–0.15 mg/kg IM, SC, or IV), meperidine (2–5 mg/kg IM, SC), morphine (0.5–1.0 mg/kg IM or SC)
P = Propofol (6–8 mg/kg)
X = Xylazine

Specific Cardiovascular Diseases

AF = Atrial fibrillation
DCM = Dilated cardiomyopathy
HCM = Hypertrophic cardiomyopathy
HT = Hyperthyroid
MR = Mitral regurgitation
PDA = Patent ductus arteriosus
PH = Pulmonary hypertension
PS = Pulmonic stenosis
SAS = Subaortic stenosis
SHP = Systemic hypertension
SSS = Sick sinus syndrome

Courtesy of Dr. Paula Moone.

about the common signs of cardiac disease, including coughing, dyspnea, weight loss, edema, exercise intolerance, or syncope (chapter 4).

PHYSICAL EXAMINATION

Important hemodynamic consequences of heart disease may be disclosed by thorough physical examination (chapter 5). The examination helps judge systemic output (e.g., pallor or prolonged capillary refill time, mental depression, abnormal jugular venous or femoral arterial pulses); uncover stenotic or incompetent cardiac valves (auscultation); detect arrhythmias (palpate arterial pulse deficits while auscultating brady- or tachyarrhythmias); uncover respiratory disease or pulmonary edema (auscultate abnormal lung sounds);

percuss abnormal fluid accumulations; and detect abnormal cardiac loading conditions (effusions, jugular venous pulses, respiratory crackles).

DATA BASE

The minimum preanesthetic cardiac data base includes (1) an electrocardiogram (ECG) with long rhythm strip, (2) thoracic radiographs, (3) a biochemical profile (for adult and geriatric animals or juveniles with congestive heart failure), and (4) serum thyroxine (T_4) assay or triiodothyronine (T_3) suppression test for older cats (>7 years of age) with suspected hyperthyroidism.

BIOCHEMICAL PROFILE AND URINALYSIS. Systemic or metabolic diseases that can adversely influence anesthesia may be uncovered. Specific tests of interest include serum electrolytes (Na^+, K^+, Cl^-, Ca^{2+}), renal indices (BUN, creatinine), serum albumin, liver enzymes (alanine aminotransferase, aspartate aminotransferase, serum alkaline phosphatase), and serum glucose. Cardiac arrhythmias and poor myocardial performance may be associated with electrolyte imbalances.[2, 3] Hypercalcemia may indicate paraneoplastic syndromes caused by neoplasia. Elevated BUN and creatinine may suggest low cardiac output, especially in animals with systolic (i.e., pumping) dysfunction or primary renal insufficiency. Prerenal azotemia is common in pets with decompensated heart failure. Renal insufficiency can be exacerbated by hypotension with prolonged anesthesia, especially if renal dysfunction is already present.[4] Anesthetic agents should be selected that minimally decrease systemic blood pressure, and they should be combined with intravenous volume expansion to maintain renal perfusion. Elevations of liver enzymes may occur from chronic passive liver congestion caused by heart failure and with feline hyperthyroidism. Decreased serum albumin levels may indicate liver dysfunction or protein-losing disease. With heart failure, it may contribute to peripheral and pulmonary edema formation. The dosage of highly protein-bound drugs may need to be reduced owing to an increase in the unbound active drug fraction.[5] Urinalysis should accompany any geriatric data base.

HEMOGRAM. Anemia can impair oxygenation during anesthesia; polycythemia increases blood viscosity, decreases tissue oxygenation, and often indicates significant right-to-left shunting of blood. Packed cell volume and total protein give an indication of hydration status. Elevated white blood cell counts may indicate stress, infection, or inflammatory diseases. Cellular atypia may suggest systemic disorders (leukemia, heartworms [eosinophilia and basophilia], or lead toxicity [basophilic stippling of reticulocytes and nucleated red blood cells]).

BLOOD GAS ANALYSIS. Arterial and venous blood gas analysis can indicate metabolic status and ventilatory capacity and provide evidence for the presence of shunts. Metabolic acidosis may result from poor tissue perfusion and warrant measures to improve cardiac output. Base deficits can be detected and corrected. Ventilatory support, either before or immediately after anesthetic induction, may help maintain normocapnia if respiratory acidosis is present. Metabolic alkalosis, often accompanied by hypokalemia, is a potential complication of chronic diuretic therapy.[6]

SERUM THYROID HORMONE DETERMINATION. Untreated hyperthyroidism poses increased anesthetic risk. Serum T_4 concentration should be measured in older cats (> 7 years of age) suspected of being thyrotoxic (chapter 34). Hyperthyroidism is associated with heart failure and arrhythmias.[6a]

ELECTROCARDIOGRAM. The *ECG* records heart rate and rhythm; records nonspecific changes with certain acid-base and electrolyte imbalances, hypoxia, or myocardial infarction; and implies cardiac chamber enlargement. Certain arrhythmias confer increased anesthetic risk, especially when combined with the depressant effects of anesthetics. These include persistent ventricular tachycardias (especially those nonresponsive to antiarrhythmic therapy); heart rates less than 60 beats per minute in dogs and less than 80 in cats that do not increase in response to anticholinergics; or right bundle branch block that develops as a manifestation of progressive heart disease. Symptomatic bradycardias may require preanesthetic placement of a temporary intravenous pacemaker to maintain cardiac output, especially during anesthesia for permanent pacemaker implantation.[7]

THORACIC RADIOGRAPHS. Chest films indicate cardiomegaly and vascular perfusion; confirm and delineate respiratory and heartworm disease; and disclose the presence of pulmonary edema, pleural effusion, masses, or other cardiopulmonary disorders.

ECHOCARDIOGRAPHY. Valuable information can be obtained about cardiac structure and function. This is especially useful for congenital heart disease, pericardial disease, feline myocardial disorders, a number of acquired cardiac conditions, and when pleural effusion obscures radiographic evaluation of the cardiac silhouette.

ADDITIONAL INFORMATION. Noninvasive blood pressure measurement, angiography, or cardiac catheterization is sometimes required.

PREOPERATIVE PATIENT PREPARATION

The patient should be stabilized before induction of anesthesia. Serious arrhythmias should be corrected whenever possible. It is important to establish a stable rhythm that maximizes cardiac output and minimizes the potential of malignant arrhythmia development. Before administering antiarrhythmic drugs, either systemic or metabolic abnormalities or concurrent medication responsible for the rhythm disturbance should be discovered and corrected. The choice of appropriate fluid therapy will help maintain appropriate electrolyte balance and maintain intravascular volume. Correct administration rates and volumes will help avoid pulmonary edema in cardiac patients and maintain adequate preload in volume-depleted animals.

INTERCURRENT DRUG THERAPIES

A rule of thumb for deciding the necessity for concurrent drug therapy is to continue drugs if (1) they have improved the patient's condition, (2) they have produced hemodynamic or metabolic stability, or (3) drug discontinuation could be associated with adverse effects or patient instability. The concurrent use of drugs with significant protein binding may decrease the required dose of certain anesthetic drugs, such as barbiturates or diazepam.[5]

INOTROPIC SUPPORT

For enhanced preoperative or intraoperative inotropic support, the sympathomimetic agents dopamine or dobutamine can be administered by intravenous constant rate infusion. These drugs are more potent than digitalis, and their cardiovascular effects are more easily controlled (chapters 12, 15).[8] In animals receiving digitalis glycosides, drugs should be continued prior to anesthesia if they are controlling supraventricular arrhythmias or helping maintain cardiac compensation. It is important to maintain normal serum potassium levels in the digitalized patient to avoid exacerbating toxicity.

BETA-ADRENERGIC BLOCKING AGENTS

Propranolol, atenolol, and similar drugs are used to treat hypertrophic cardiomyopathy and tachyarrhythmias, and as palliative therapy for tetralogy of Fallot. Certain cautions must be considered with these agents regarding anesthesia. For example, their antiadrenergic activity can add to the negative inotropic effects of inhalation agents. Bronchoconstriction may be exacerbated in asthmatics or in patients with chronic obstructive pulmonary disease because bronchodilation, a response to β_2-adrenergic stimulation, is blocked by propranolol. But because sudden withdrawal of propranolol can result in tachycardia, arrhythmias, and hypertension,[9] it should be continued prior to anesthesia with appropriate patient monitoring. If necessary, the β-blockade of propranolol may be overcome intraoperatively with β-adrenergic agonists, such as dopamine or dobutamine.[8]

CARDIOGENIC PULMONARY EDEMA

This should be treated preoperatively with furosemide, vasodilators, and positive inotropes where indicated (chapter 13).[6] Intraoperative measures to improve gas exchange after endotracheal intubation may be beneficial and include supplemental oxygen administration, bronchodilators, and suction. Positive end-expiratory pressure (PEEP) and positive-pressure ventilation (PPV) after intubation may also help increase the arterial oxygen content by reducing alveolar flooding by edema.[10]

CIRCULATORY SHUNTS

These may have a direct effect on induction of anesthesia. *Left-to-right shunts,* such as a large ventricular septal defect or patent ductus arteriosus, cause pulmonary hyperperfusion. Rapid uptake of inhalation agents and induction may result, causing acute central nervous system (CNS) depression. A left-to-right shunt may cause a delay in anesthetic effect after administration of an intravenous induction agent because a portion of the bolus is recirculated through the pulmonary vasculature before making its way to the central nervous system (CNS).[5] Fatal overdosage could result if the initial bolus is promptly followed by additional drug administration before adequate time for induction has elapsed.

Right-to-left shunts, such as tetralogy of Fallot, produce pulmonary hypoperfusion. Decreased pulmonary blood flow may result in slow induction when using inhalation agents. By contrast, intravenous induction agents produce a rapid onset of action, because drug boluses partially bypass the pulmonary circuit, travel-

ing immediately to the systemic circulation and the CNS.[5] Moreover, anesthesia may exacerbate a right-to-left shunt by lowering the systemic blood pressure.[11] Maintaining a stable and adequate mean systemic blood pressure is essential to avoid this problem.

PERICARDIAL EFFUSION

Pericardiocentesis is recommended prior to anesthetic induction when significant pericardial effusion or cardiac tamponade is documented. Pericardial effusion may cause severe ventricular underfilling, decrease cardiac output, lower systemic blood pressure, alter coronary blood flow, and predispose to myocardial ischemia.[12] Anesthesia under these conditions could lead to ventricular fibrillation. Moreover, the cardiac output of patients with pericardial effusion is often highly dependent on heart rate, since stroke volume is limited by an underfilled left ventricle. Therefore, avoidance of drugs that result in bradycardia and prevention of deep anesthetic levels are important.

PLEURAL EFFUSION AND ASCITES

Severe effusions can be detrimental to the anesthetized animal. Diaphragmatic pressure from ascites may interfere with thoracic expansion and ventilation. Severe pleural effusion will restrict lung expansion. Preoperative drainage of a portion of the effusion will reduce associated respiratory distress.

PNEUMOTHORAX

When pneumothorax is severe, lung excursion and related ventilation are impaired. Preoperative removal by aspiration is required.

ANESTHETIC CONSIDERATIONS

ESTABLISHING ANESTHETIC RISK

Once the patient is medically evaluated and stabilized, the severity or stage of cardiac disease and the relative risk of anesthesia are determined. The American Society of Anesthesiologists (ASA) has developed a classification of patient risk category to decide the individual risk of anesthesia and appropriate drug strategy (Table 38–2). A classification scheme devised by the New York Heart Association for functional phases of heart failure in humans has been modified and adapted for dogs[13] (chapter 12).

Class I heart failure is characterized by normal exercise tolerance and no overt clinical signs of heart disease. These animals would be placed in ASA category 2. Virtually any drug among the list of premedicants or induction agents (Tables 38–3 and 38–4) would be suitable, including potent inhalation agents and nitrous oxide.

Class II heart failure is characterized by occasional coughing and dyspnea after strenuous exercise, but the animal is usually comfortable at rest. These patients can be placed in ASA category 3. Premedication should be confined to diazepam, narcotics, or ketamine. Induction can be carried out with intravenous diazepam/ketamine, narcotics, low dosages of thiobarbiturates or propofol, thiopental/lidocaine, or etomidate. Any of the potent agents are acceptable, but it may be safer to supplement anesthesia with narcotics rather than to maintain anesthesia solely with inhalation agents.

Class III heart failure patients cough or become dyspneic after minimal exercise and at night. Class IV heart failure describes fulminant congestive heart failure that is clinically obvious at rest. Class III and early Class IV heart failure patients become grouped under ASA category 4. Great care must be taken for successful anesthesia in these patients. Diazepam premedication in dogs and low doses of ketamine in cats could be used if necessary. Narcotic supplementation with lower doses of inhalation agents will maintain an adequate depth of anesthesia.

Late Class IV heart failure animals are at very high risk and are placed in ASA category 5. The potential benefit to be derived from surgery must be weighed carefully against the risk of anesthesia. In dogs, narcotic agents are the safest, combined with neuromuscular blocking drugs and local anesthesia, when possible. Lower dosages are necessary when heart failure becomes more advanced.

TABLE 38–2
American Society of Anesthesiologists Risk Categories for Anesthesia

ASA Category	Patient Description
1	Normal patient; no organic disease
2	Patient with mild systemic disease
3	Patient with severe systemic disease limiting activity but not incapacitating
4	Patient with incapacitating systemic disease that is a constant threat to life
5	Moribund patient not expected to live 24 hours with or without surgery
E	Emergency operation, designed by placing E after appropriate category

TABLE 38–3
Premedicants for the Cardiovascular Patient

Drug	Dosage (mg/kg)	Dog/Cat	Route	Class of Heart Failure	ASA Category
Atropine	0.02–0.06	Both	IM/IV	I–III	2–4
Glycopyrrolate	0.005–0.01	Both	IM/IV	I–III	2–4
Lenperone	0.2–1.0	Both	IM	I	2
Diazepam	0.2–0.5	Both	IV	I–IV	2–5
Ketamine	5–10	Cat	IM	I–IV	2–5
Innovar-Vet	0.1	Dog	IM	I–IV	2–5
Morphine	0.2–0.5	Dog	IM	I–IV	2–5
Oxymorphone	0.05–0.1	Both	IM	I–IV	2–5
Butorphanol	0.1–0.4	Both	IM	I–IV	2–5
Buprenorphine	0.005–0.02	Both	IM	I–IV	2–5

IM, intramuscular; IV, intravenous.

ANESTHESIA AND THE HIGH-RISK PATIENT

Anesthetic agents may directly affect cardiac myocardial, mechanical, or electric activity. Alternatively, they may indirectly influence cardiac function through their action on the nervous system or vasculature (Tables 38–5 and 38–6). Normally, animals have a large cardiovascular reserve that allows the stress of anesthesia to be well tolerated. However, patients with cardiovascular compromise may have exhausted much of this reserve and are often unable to compensate for the effects of anesthetic agents. In these cases, drug dosages must be carefully titrated to the minimal amount required.

There are many ways to induce and maintain anesthesia in the compromised, high-risk cardiac patient. Balanced anesthesia employing a combination of several drugs may be the best approach. It permits the use of lower doses, minimizes cardiovascular depression, and allows for adjustment of variables, such as analgesia, muscle relaxation, and hypnosis. Clinical evaluation of anesthetic drug effects on cardiovascular function should focus on changes in heart rate and rhythm (ECG monitoring), arterial blood pressure, cardiac output (e.g., capillary refill time, mucous membrane color, urine output), and contractility (inferred by apex beat and heart sounds). Indirect blood pressure measurement is becoming increasingly available (chapter 35).

PREANESTHETIC DRUGS

Premedication can decrease pain and anxiety and thus reduce adverse changes in autonomic tone. Doses are titrated according to disease. In cardiac patients, routinely administered drugs include opioids (dogs) and benzodiazepines. Agents generally avoided include acepromazine, Telozol, α_2-agonists (xylazine), and high-doses (>5 mg/kg) of ketamine in cats (see Table 38–1).[13a]

ANTICHOLINERGICS

Atropine and glycopyrrolate are anticholinergic premedicants used mainly to increase heart rate and reduce salivation (see Table 38–2). These agents exert peripheral vagolytic as well as transient central vagomimetic effects. Peripherally, their vagolytic effects in-

TABLE 38–4
Intravenous Agents for the Cardiovascular Patient

Drug	Dosage (mg/kg)	Dog/Cat	Class of Heart Failure	ASA Category
Thiopental	8–15	Both	I–II	2
Thiopental/lidocaine	4 (each drug)	Dog	I–III	2–3
Etomidate	1–2	Both	I–IV	2–4
Propofol	2–6	Both	I–IV	2–4
Diazepam (2.5 mg/ml) + Ketamine (50 mg/ml)	0.1–0.5 ml/kg*	Both	I–IV	2–4
Oxymorphone	0.025–0.1	Both	I–IV	2–5
Fentanyl	0.002–0.006	Dog	I–IV	2–5
Innovar-Vet	0.5 ml/kg	Dog	I–IV	2–5
Pancuronium	0.04	Both	I–IV	2–5
Atracurium	0.15–0.50	Both	I–IV	2–5
Vecuronium	0.05–0.25	Both	I–IV	2–5

*Dose in milliliters of 1:1 diazepam:ketamine mixture.

TABLE 38-5
Clinical Effects of Common Premedicants

Drug	Rate & Rhythm Changes	Contractility	Blood Pressure	Myocardial Oxygen Consumption	Cardiac Output
Anticholinergics	Transient AVB; sinus tachycardia	Slight ↑	NC	↑	↑
Phenothiazines	Reflex tachycardia; antiarrhythmic	↓	↓	↑	↑
Butyrophenones	Reflex tachycardia; antiarrhythmic	Slight ↓	NC	NC	↓
Benzodiazepines	NC	NC	NC	↓	NC
Xylazine	Bradycardia; 1°, 2° AVB; arrhythmogenic	↓	Initial ↑, then ↓	↓	↓
Ketamine	Sinus tachycardia	↑	↑	↑	↑
Morphine	Bradycardia; 1°, 2° AVB	NC	May ↓ (histamine)	NC	May ↓ (bradycardia)
Meperidine	Bradycardia; 1°, 2° AVB; reflex tachycardia	↓	↓	↓	NC
Oxymorphone	Bradycardia; 1°, 2° AVB	NC	NC	NC	May ↓ (bradycardia)
Fentanyl	Bradycardia; 1°, 2° AVB	NC	NC	NC	May ↓ (bradycardia)
Innovar-Vet	Bradycardia; 1°, 2° AVB	NC	NC	NC	May ↓ (bradycardia)

NC, no change; ↑, increase; ↓, decrease; 1°, first degree; 2°, second degree; AVB, atrioventricular block.

crease the rate of sinoatrial (SA) node discharge and reduce atrioventricular (AV) node conduction time. As heart rate increases, cardiac output and blood pressure may become elevated secondarily. Arrhythmias may occur due to altered AV conduction. For example, when atropine is administered intravenously, transient heart rate slowing and first- or second-degree atrioventricular (AV) block may result from initial central nervous system vagomimetic activity.[14]

A major indication for anticholinergic use is development of hemodynamically severe bradycardia. Anticholinergic premedication is also indicated in animals whose cardiac output is highly rate dependent, such as may occur with severe pericardial disease. The advantage of increased stable heart rate caused by anticholinergics must be weighed against their vagolytic effects causing inability to detect early anesthetic-induced reduction in heart rate that could indicate deepening anesthesia. Furthermore, excessive increases in heart rate from anticholinergics may critically elevate myocardial oxygen consumption and predispose to arrhythmias.

PHENOTHIAZINES

Phenothiazines provide excellent tranquilization but should be used with great caution in the cardiac-compromised patient. Phenothiazines are potent α-adrenergic and dopaminergic blocking drugs.[15] They have a direct negative inotropic effect, and their action on α-adrenergic receptors in vascular smooth muscle results in vasodilation and hypotension. Hypotension is often followed by reflex tachycardia, which secondarily increases myocardial oxygen consumption. Rarely, acepromazine can cause profound bradycardia with first- or second-degree AV block. Although phenothiazines

TABLE 38-6
Clinical Effects of Common Intravenous Agents

Drug	Rate & Rhythm Changes	Contractility	Blood Pressure	Myocardial Oxygen Consumption	Cardiac Output
Thiobarbiturates	Reflex tachycardia; bigeminy; ventricular ectopia	↓	↓	↑	↓
Thiopental/ lidocaine	Reflex tachycardia; antiarrhythmic	↓	Slight ↓	↑	↓
Etomidate	NC	NC	Slight ↓	NC	NC
Propofol	Variable	Slight ↓	↓	↓	Slight ↓
Innovar-Vet	Bradycardia; 1°, 2° AVB	↑	NC	NC	May ↓ (bradycardia)
Diazepam/ketamine	Rate increase	↑	↑	↑	↑
Pancuronium	Rate increase; ventricular arrhythmias	NC	↑	↑	↑
Atracurium	Rate increase at high dose due to histamine release	NC	May ↓ (histamine)	NC	NC
Vecuronium	NC	NC	NC	NC	NC

↑, Increase; ↓, decrease; NC, no change; 1°, first degree; 2° second degree.

are antiarrhythmic and protect the myocardium against both barbiturate- and epinephrine-induced arrhythmias,[16] this property must be weighed against their deleterious effects.

BUTYROPHENONES

Like phenothiazines, butyrophenones are α-adrenergic blocking drugs and can confer protection to the myocardium from catecholamine-induced arrhythmias.[17] Cardiovascular depressant properties of butyrophenones are similar to those of the phenothiazine tranquilizers but are less severe.[18] Although the butyrophenone tranquilizers have fewer deleterious side effects than the phenothiazines, they should be used with caution and the dose titrated to produce the desired effect. Droperidol, in combination with fentanyl (Innovar-Vet), is the butyrophenone tranquilizer most commonly used in dogs.

BENZODIAZEPINES

Diazepam is a benzodiazepine derivative that can be safely used in the cardiac patient. It produces minimal cardiovascular depression, resulting in little change in heart rate, contractility, blood pressure, or cardiac output.[19] Diazepam may improve coronary blood flow and at the same time decrease myocardial oxygen consumption.[20] It has an antiarrhythmic effect because of its ability to decrease sympathetic tone centrally, and it is compatible with most other anesthetic agents. However, when used in combination with high doses of fentanyl, diazepam significantly decreases stroke volume, cardiac output, and systemic blood pressure.[21] Owing to the solubility characteristics of diazepam, it is formulated in a 40 percent propylene glycol base. Although rapid intravenous administration of propylene glycol can be cardiotoxic and cause hypotension and bradycardia, these effects are rarely observed with diazepam.

XYLAZINE

Xylazine is a poor choice as a sedative in compromised cardiac patients. An α-agonist, xylazine causes central reduction of sympathetic tone. After administration, vagally mediated bradycardia and reduction in contractility occur. Its α-agonistic effects result in transient hypertension because of increased peripheral vascular resistance, but this is followed by prolonged hypotension. Cardiac output is adversely affected through negative inotropy, bradycardia, and increased afterload.[22] Xylazine potentiates arrhythmias and increases myocardial sensitivity to catecholamines.[16]

KETAMINE

Appropriate for most cardiac diseases, ketamine combined with diazepam provides excellent and safe induction. Because of its ability to cause excitement, delirium, and convulsions, ketamine should be combined with a CNS sedative (e.g., diazepam), particularly in dogs. The direct myocardial effect of ketamine is to decrease contractility. However, it often acts as a positive inotrope through its sympathetic nervous system effects that override its direct myocardial depressant property.[23, 24] An increase in heart rate, myocardial oxygen consumption, cardiac output, and systemic blood pressure can result. Ketamine may exert myocardial depressant effects on the cardiac patient whose sympathetic tone is already high due to cardiac decompensation. Ketamine (1 to 4 mg/kg intravenously) is also used as a short-term tranquilizer in cats, although it may precipitate or exacerbate extrasystoles when administered to cats with advanced hyperthyroidism or severe heart failure.

NARCOTICS

Narcotics are useful in dogs for premedication, induction, and maintenance of anesthesia. They have predictable but minimal hemodynamic effects in the critically ill animal. Analgesia is excellent and, in most instances, the level of provided sedation-hypnosis is good. A narcotic antagonist (e.g., naloxone) may induce arousal of the severely depressed animal or reversal of respiratory depression.

Morphine may cause bradycardia by inducing central vagal stimulation. This effect can be prevented with administration of anticholinergics, if necessary. Myocardial performance is maintained with morphine, although histamine release may be stimulated. This can decrease peripheral vascular resistance and potentially contribute to hypotension.[25, 26]

Meperidine has one tenth the analgesic potency of morphine but is a much greater cardiovascular depressant.[27] It decreases myocardial contractility directly, causes peripheral vasodilation, and mediates hypotension.

Oxymorphone is commonly used in combination with tranquilizers as a neuroleptanalgesic agent in the dog or cat. Oxymorphone is ten times more potent an analgesic than morphine. Its use reduces the required dosage of other agents necessary for induction. Oxymorphone is an excellent intraoperative drug in the dog or cat for supplementing a light plane of anesthesia, provided the animal is monitored for bradycardia.

Fentanyl is also a useful narcotic for intraoperative anesthetic supplementation. Its rapid onset of action is advantageous. Fentanyl may cause dysphoria and muscle rigidity when used in the conscious dog. Therefore, it is most often given in combination with droper-

idol in the neuroleptanalgesic combination, Innovar-Vet. Fentanyl with droperidol provides excellent cardiovascular stability, whether administered intramuscularly for sedation or intravenously, as long as bradycardia is prevented or alleviated by anticholinergic administration (e.g., atropine). Innovar-Vet may increase peripheral vascular resistance, acutely increase systemic blood pressure, and significantly increase left ventricular contractility and coronary blood flow.[28]

The agonist-antagonist type of narcotics, such as butorphanol and buprenorphine are generally safe and effective in dogs and cats with cardiovascular disease. Buprenorphine's duration of action is longer than that of other commonly used opioids. Both agents cause relatively less severe respiratory depression compared with most narcotics.[27]

DRUGS USED FOR ANESTHETIC INDUCTION

Injectable anesthetic doses should be as low as possible to minimize cardiorespiratory depression. Preoxygenation with 100 percent oxygen for 3 to 5 minutes may be performed for animals who will tolerate a face mask. Large doses of thiobarbiturates cause marked cardiorespiratory depression. Thiobarbiturate risks are reduced when dosed at less than 8 mg/kg IV. Mask induction with halothane or isoflurane may cause marked cardiovascular depression associated with induction doses and is not recommended.[13a]

A number of drugs or drug combinations may be used to induce anesthesia (see Tables 38–1, 38–3, and 38–6). Intravenous Innovar-Vet and diazepam with ketamine have already been mentioned.

THIOBARBITURATES

These are the most frequently administered intravenous induction agents. They are used most safely in many compromised animals when low doses are given by slow intravenous bolus, but adverse cardiovascular effects can occur.[29] For example, thiobarbiturate boluses may cause impaired myocardial contractility and vasodilation. This may lead to peripheral pooling of venous blood and result in decreased ventricular filling pressures and an overall decrease in cardiac output. The resultant hypotension and decreased cardiac output cause a reflex tachycardia through sympathetic nervous system stimulation, which increases myocardial oxygen consumption. The development of arrhythmias, especially ventricular bigeminy or other ectopia, can occur.[30] The pet with poor systolic ventricular function or unstable cardiac rhythm is a poor candidate for thiopental induction. Additional major side effects are respiratory depression and apnea.[30a] Because the severity of adverse drug effects is directly correlated with dose, small doses of thiobarbiturates may be tolerated for induction in the depressed or well-sedated animal.

Intravenous use of a thiobarbiturate with lidocaine in dogs may offer a safe alternative to induction with thiobarbiturates alone.[31] Lidocaine reduces the amount of thiobarbiturate required for induction by approximately 50 percent. Additionally, lidocaine has ventricular antiarrhythmic properties and may diminish reflex responses to endotracheal intubation (i.e., laryngospasm and tachycardia). The two drugs should not be mixed in the same syringe to avoid precipitation.

ETOMIDATE

This intravenous hypnotic agent has potential value for anesthetic induction in dogs or cats with cardiovascular compromise. Bolus administration produces a clinical effect similar to that of the thiobarbiturates, but with little or no hemodynamic change. Cardiac contractility is not adversely affected. A small reduction of arterial blood pressure occurs, but mean coronary blood flow is preserved.[32]

PROPOFOL

A phenol derivative that produces rapid onset, intravenous propofol causes short-duration, noncumulative anesthesia in dogs and cats.[33] Cardiovascular effects are similar to those of thiobarbiturates and are dose-related. Propofol induction significantly decreases systemic blood pressure. Reductions of 20 to 40 percent have been reported.[33a] This is primarily due to a decrease in vascular resistance.[34] Direct myocardial depressant effects are less than those produced by the thiobarbiturates.[35, 36] Propofol (6.6 mg/kg IV) given over 60 seconds, followed by halothane or isoflurane inhalant anesthesia, is safe and effective in healthy dogs.[36a] Animals with good ventricular function and normal cardiovascular reserve undergo little change in cardiac output when given propofol.[34] However, it should be used with caution when impaired cardiovascular function and pre-existing hypotension are present,[37] and it should be reserved for animals that are hemodynamically stable.

Respiratory depression and apnea are serious side effects, particularly when propofol is administered at rapid rates of infusion. Apnea increases in a dose-dependent manner at dosages greater than 14 mg/kg.[37a] Small doses may be tolerated and adequate for induction of the depressed or well-sedated animal.

DRUGS USED FOR ANESTHETIC MAINTENANCE

Anesthetic maintenance can be achieved in dogs and cats using inhalation agents titrated to effect. In

dogs, a combination of high-dose narcotics with skeletal muscle relaxants can also be used (see Table 39–1).

INHALATION AGENTS

Maintenance with inhalation agents has the advantages of ease of administration and ability to control the level of anesthesia. These agents are compatible with essentially all other anesthetic drugs. Their cardiovascular depressant effects are dose related. Thus, if analgesia is supplemented with the concurrent use of narcotics, low doses of inhalation agents may be highly effective, even in the high-risk small animal patient. All potent inhalation agents depress myocardial function and decrease systemic blood pressure in direct proportion to the depth of anesthesia.[38]

HALOTHANE. Because of its arrhythmogenicity and marked myocardial depressant quality, halothane should be used with caution in the cardiac patient. It decreases cardiac output and myocardial oxygen consumption[39] and sensitizes the myocardium to catecholamines. The latter effect does not appear to be dose related.[40] In fact, light planes of halothane anesthesia may exacerbate its arrhythmogenic properties due to endogenous catecholamine release in response to surgical stress.

METHOXYFLURANE. This drug depresses cardiac output and decreases total peripheral resistance, resulting in hypotension.[39] Since its cardiac depressant effects are dose related, methoxyflurane can be used successfully at reduced doses in the cardiac patient. It is an excellent analgesic even in light planes of anesthesia. Its high tissue solubility causes prolonged induction, recovery, and slow change in anesthetic depth. These properties can be disadvantageous in the critically ill patient.

ENFLURANE. Due to its cardiac depressant properties, enflurane causes a decrease in systemic blood pressure. It also reduces total peripheral resistance. Since its potency is less than that of other inhalation agents, the need to maintain animals at higher alveolar concentrations in order to achieve adequate anesthesia may increase the direct cardiodepressant effects.[39] The ability of enflurane to increase myocardial sensitivity to catecholamines is less than that of halothane.

ISOFLURANE. Isoflurane causes significant hypotension by decreasing total peripheral resistance; caution must be exercised when using it in animals with marked hypotension. At surgical planes of anesthesia, it does not alter myocardial contractility and does not sensitize the heart to catecholamine-induced arrhythmias.[39] Cardiac output is well maintained at anesthetic dosages. The margin between the lethal and anesthetic dose is the widest of any of the modern potent inhalation agents, and isoflurane is often chosen as the safest inhalation agent for animals with heart disease.[39] However, it is the most hypotensive of the inhalation agents and must be used with caution in pets with shock or hypotension. The use of 1.3 mean alveolar concentration (MAC) isoflurane in normal cats results in minimal cardiopulmonary depression, but 2.0 MAC isoflurane causes hypotension and hypercapnia and should be avoided in cats.[39a]

SERVOFLURANE. This agent has cardiovascular effects similar to those of isoflurane. Its main advantage is very low solubility, which provides rapid onset and recovery. This allows rapid changes in the plane of anesthesia in the event of poor drug tolerance in animals with decompensated heart disease. Servoflurane will cause hypotension but is not arrhythmogenic and does not cause myocardial depression at clinically used levels.[39]

NITROUS OXIDE. Beneficial for use in the cardiac patient, N_2O does not alter blood pressure by itself. While N_2O is a myocardial depressant, it reduces the concentration of required inhalation agents when used in combination with other potent inhalation anesthetics. It slightly increases sympathetic cardiac activity and provides hemodynamic stability.[39] In combination with fentanyl, it causes a marked decrease in cardiac output and systemic blood pressure.[41] Nitrous oxide should be avoided or at least discontinued 10 to 15 minutes before chest closure begins to prevent exacerbation of a pneumothorax after thoracotomy. It should be avoided in an animal with poor oxygenation preoperatively and discontinued if hypoxemia develops during the anesthetic period.

BALANCED ANESTHESIA

The advantages of classic balanced anesthesia (narcotics plus tranquilization and neuromuscular blocking agents) in dogs include (1) decreased myocardial depression, (2) maintenance of more adequate levels of systemic blood pressure, and (3) easy reversibility. However, this technique using drug combinations is complex and requires careful patient monitoring well into the postoperative period. Narcotics have been discussed in relationship to their minimal cardiovascular effects.

NEUROMUSCULAR BLOCKING DRUGS

Nondepolarizing muscle relaxants such as atracurium, vecuronium, or pancuronium are the preferred neuromuscular blocking agents in the cardiac patient (see Table 38–4). Nondepolarizing agents do not alter serum potassium levels as might occur with a depolariz-

ing neuromuscular blocker. Neither pancuronium nor vecuronium causes significant histamine release, and both are reversible postoperatively. Their cardiovascular effects include an increase in heart rate, blood pressure, and cardiac output.[42]

INTRAOPERATIVE PATIENT MONITORING

ELECTROCARDIOGRAPHIC MONITORING. The ECG should be monitored throughout anesthesia. Pharmacologic intervention is not always required for intraoperative arrhythmias. Identification of reversible factors associated with arrhythmias includes hypoxia or hypercapnia, acid-base disturbances, excess endogenous catecholamines, electrolyte abnormalities, autonomic reflexes, and anesthetics.[43]

INTRAVENOUS ACCESS SITES. These are essential in any high-risk patient undergoing anesthesia. Two IV lines facilitate rapid infusion of intravenous fluids through one catheter and drug administration through the other; they also allow for simultaneous fluid, blood, or plasma administration as necessary.

FLUID THERAPY MONITORING. The cardiac patient may be unable to receive or pump blood effectively because of poor ventricular compliance, elevated preload, or myocardial (pumping) failure. These issues must be factored into patient monitoring. An administration rate of 10 ml/kg/hr is a basic intraoperative guideline. If hypotension and poor cardiac output are evident, volume expansion may be accomplished by increasing the rate of fluid administration. Fluids are continued postoperatively until hemodynamic stability and adequate urine production are achieved. Conversely, animals with heart failure, pulmonary hypertension, and conditions inhibiting ventricular filling (e.g., pericardial tamponade, intracardiac masses) may develop congestion when receiving fluid therapy calculated for a normal patient.

URINE OUTPUT. This can be a useful indicator of adequate fluid therapy. Renal perfusion is sensitive to changes in autonomic tone. Urine output depends on maintaining a mean arterial blood pressure of at least 70 mmHg.[44] Reduced urine output results when renal perfusion and renal function are inadequate. This should prompt measures to improve renal perfusion (e.g., decreasing anesthetic depth, volume expansion to correct hypotension, positive inotropic agents to improve cardiac output). Dopamine is used as a renal vasodilator at low dosages (1 to 2 μg/kg/min), improving renal perfusion and urine production.

CENTRAL VENOUS PRESSURE. Monitoring CVP can provide valuable information to guide the rate of fluid administration during surgery. Normal CVP is 0 to 5 cm H_2O. If the cardiac output appears adequate (i.e., normal peripheral perfusion, strong arterial pulses, and cardiac apex beat suggesting normal arterial blood pressure), a satisfactory cardiovascular state may exist. If fluid administration increases CVP more than 8 to 10 cm H_2O, fluid overload or cardiac failure may be evident. Measurements in the range of 15 to 20 cm H_2O are generally too high. Fluid administration may need to be reduced or temporarily discontinued. Measures to improve cardiac function include decreasing anesthetic depth and positive inotrope infusion (e.g., dopamine or dobutamine). Administration of colloid rather than crystalloid fluids may decrease the likelihood of pulmonary edema formation, provided the alveolar-capillary membrane is intact. Furosemide should be given intravenously if pulmonary edema develops. A low CVP generally indicates hypovolemia. Fluid administration should be increased to elevate CVP to the upper limit of normal.[45, 46]

ARTERIAL BLOOD PRESSURE MONITORING. This is beneficial in the anesthetized cardiac patient and is the best way of assessing whether adequate tissue perfusion pressures are being maintained (chapter 35). Heart rate and pulse pressure correlate poorly with actual arterial blood pressures and could be misleading when relied on solely as a perfusion estimate.[46, 47] Arterial pressure alone is not an indicator of cardiac output. Indirect blood pressure can be monitored using oscillometric devices (Dinamap, Criticon, Tampa, FL),[48] which work best on medium and large dogs but less consistently in small dogs and in cats.[49] Commercial devices using ultrasonic kinetoarteriography (Doppler ultrasound) are also available (Arteriosonde, Hoffman–La Roche, Cranberry, NJ).[50, 51]

CONTROLLED VENTILATION. This is necessary during thoracotomy and prolonged surgical procedures. It is important to maintain a proper inspiratory-to-expiratory time ratio. Prolonged inspiratory times cause extended periods of positive pressure within the thoracic cavity, decreasing cardiac venous return. An inspiratory-expiratory ratio of 1:2 to 1:4 is therefore recommended to avoid adverse effects on cardiac output.

BLOOD GAS MONITORING. To help assess the effectiveness of ventilation, blood gas monitoring is helpful. If hypercapnia occurs, ventilation should be improved by increasing the number of breaths per minute or tidal volume (i.e., the amount of air moving into the lungs with each inspiration). Inadequate oxygenation with normal arterial PCO_2 ($PaCO_2$) can be caused by certain cardiac shunts, or it could indicate a ventilation-

perfusion mismatch as occurs with low cardiac output states or lung pathology (e.g., pulmonary edema).[52]

PULSE OXIMETRY. This provides a means for continuous noninvasive monitoring of patient oxygenation. Pulse oximeters determine the percent of oxygen saturation of hemoglobin in arterial blood by detecting differences in red and infrared light absorbance in the pulsatile component of tissue blood flow.[53] The percent of oxygen saturation of hemoglobin in arterial blood indirectly reflects the patient's PaO_2. Currently, pulse oximeters are coming on the market (PALCO Laboratories, Santa Cruz, CA; Sensor Devices Inc., Waukesha, WI) with probes designed specifically for veterinary application.

CLINICAL PATHOLOGY. Hematocrit, total protein, platelets, and clotting profiles may need to be assessed. Surgical blood loss can become a critical factor during anesthetic management. Whole blood for transfusion should be obtained prior to the anesthetic period whenever significant blood loss is anticipated. Fresh plasma transfusion alone may be sufficient with hypoproteinemia, thrombocytopenia, or clotting disorders.

PATIENT MONITORING

Close observation of heart rate and rhythm, mucous membrane color and refill time, arterial pulse pressure and quality, and respiratory rate and pattern are essential. Body temperature must be followed. Hypothermia is a deleterious consequence of anesthesia in many cats and dogs and may occur during or after surgical completion. Animals should be kept warm postoperatively with externally applied heat and warmed fluids. Shivering uses a great deal of metabolic energy. Electrocardiographic monitoring is essential and may need to be continued postoperatively for some animals. Emergency resuscitative equipment and drugs should be on hand at all times during and after anesthesia (chapter 21). Arterial blood pressure, pulse oximetry, and central venous pressure monitoring may be required in decompensated animals. Additionally, intravascular fluid volume (PCV, total solids), urine output (ideal, > 1 ml/kg/hr), and renal function may need to be assessed. Progressive intraoperative or postoperative decline may require decreasing anesthetic depth, ventilatory support, and expanding circulating blood volume (IV crystalloid or colloid fluids; blood or blood components). Inotropes (dopamine, dobutamine) may be required.

REFERENCES

1. Bull AP. The anesthetic evaluation and management of the surgical patient with heart disease. Surg Clin North Am 63:1035, 1983
2. Stark DCC, Silvay G. Anesthetic management for cardiac surgery not requiring cardiopulmonary by-pass. Int Anesthesiol Clin 17:71, 1979

2a. Wilkund RA, Rosenbaum SH. Anesthesiology. First of two parts. N Engl J Med 337:1132, 1997

3. Vaughan RS, Lunn JN. Potassium and the anaesthetist. Anaesthesia 28:118, 1973
4. Maddern PJ. Anaesthesia for the patient with impaired renal function. Anaesth Intensive Care 11:321, 1983
5. Saidman LJ. Uptake, distribution and elimination of barbiturates. *In* Eger EI (ed): Anesthetic Uptake and Action. Baltimore, Waverly Press, 1974, p 270
6. Bonagura JD. Fluid and electrolyte management of the cardiac patient. Vet Clin North Am 12:501, 1982
7. Bonagura JD, Helphrey ML, Muir WW. Complications associated with permanent pacemaker implantation in the dog. J Am Vet Med Assoc 182:149, 1983
8. Pennock JL. Perioperative management of drug therapy. Surg Clin North Am 63:1049, 1983
9. Muir WW, Sams R. Clinical pharmacodynamics and pharmacokinetics of beta-adrenoceptor blocking drugs in veterinary medicine. Compend Cont Ed 6:156, 1984
10. Sibbald WJ, Calvin JE, Holliday RL, et al. Concepts in the pharmacologic and nonpharmacologic support of cardiovascular function in critically ill surgical patients. Surg Clin North Am 63:455, 1983
11. Bland JW, Williams WH. Anesthesia for treatment of congenital heart defects. *In* Kaplan JA (ed): Cardiac Anesthesia. New York, Grune & Stratton, 1979, p 281
12. Shabetai R, Fowler NO, Guntheroth WG. The hemodynamics of cardiac tamponade and constrictive pericarditis. Am J Cardiol 26:480, 1970
13. Ettinger SJ, Suter PF. Canine Cardiology. Philadelphia, WB Saunders, 1970

13a. Hellyer PW. Anesthesia in patients with cardiopulmonary disease. *In* Bonagura JD, Kirk RW (eds): Kirk's Current Veterinary Therapy XI. Philadelphia, WB Saunders, 1992, p 655

14. Muir WW. Effects of atropine on cardiac rates and rhythms in dogs. J Am Vet Med Assoc 172:917, 1978
15. Baldessarini RJ. Drugs used in the treatment of psychiatric disorders. *In* Gilman AG, Rall TW, Nies AS, et al (eds): Goodman and Gilman's The Pharmacologic Basis of Therapeutics. 8th ed. New York, Pergamon Press, 1990, p 383
16. Muir WW, Werner LL, Hamlin RL. Effects of xylazine and acetylpromazine upon induced ventricular fibrillation in dogs anesthetized with thiamylal and halothane. Am J Vet Res 36:1299, 1975
17. Bertolo L, Novakovic L, Penna M. Antiarrhythmic effects of droperidol. Anesthesiology 37:529, 1972
18. Hall LW, Clarke KW. Veterinary Anaesthesia. 9th ed. London, Bailliere Tindall, 1991, p 51
19. Abel RM, Staroscik RN, Reis RL. The effects of diazepam (Valium) on left ventricular function and systemic vascular resistance. J Pharmacol Exp Ther 173:364, 1970
20. Abel RM, Reis RL, Staroscik RN. Coronary vasodilatation following diazepam (Valium). Br J Pharmacol 38:620, 1970
21. Reves JG, Kissin I, Fournier SE. Additive negative inotro-

pic effect of a combination of diazepam and fentanyl. Anesth Analg 63:97, 1984
22. Klide AM, Calderwood HW, Soma LR. Cardiopulmonary effect of xylazine in dogs. Am J Vet Res 36:931, 1975
23. Wright M. Pharmacologic effects of ketamine and its use in veterinary medicine. J Am Vet Med Assoc 180:1462, 1982
24. Haskins SC, Farver TB, Patz JD. Ketamine in dogs. Am J Vet Res 46:1855, 1985
25. Vatner SF, March JD, Swain JF. Effects of morphine on coronary and left ventricle dynamics in conscious dogs. J Clin Invest 55:207, 1975
26. Roscow CE, Moss J, Philbin DM, et al. Histamine release during morphine and fentanyl anesthesia. Anesthesiology 56:93, 1982
27. Thurmon JC, Tranquilli WJ, Benson GJ. Lumb & Jones Veterinary Anesthesia. 3rd ed. Baltimore, Williams & Wilkins, 1996, p 183
28. Buckhold DK, Erickson HH, Lumb WV. Cardiovascular response to fentanyl-droperidol and atropine in the dog. Am J Vet Res 38:479, 1977
29. Conway CM, Ellis DB. Hemodynamic effects of short-acting barbiturates. Br J Anaesth 41:534, 1969
30. Muir WW. Electrocardiographic interpretation of thiobarbiturate-induced dysrhythmias in dogs. J Am Vet Med Assoc 170:1419, 1977
30a. Quandt JE, Robinson EP, Rivers WJ, et al. Cardiorespiratory and anesthetic effects of propofol and thiopental in dogs. Am J Vet Res 59:1137, 1998
31. Bjorling DE, Rawlings CA. Induction of anesthesia with thiopental-lidocaine combination in dogs with cardiopulmonary disease. J Am Anim Hosp Assoc 20:445, 1984
32. Gooding JM, Weng JT, Smith RA, et al. Cardiovascular and pulmonary responses following etomidate induction of anesthesia in patients with demonstrated cardiac disease. Anesth Analg 58:40, 1979
33. Weaver BMQ, Raptopoulos D. Induction of anaesthesia in dogs and cats with propofol. Vet Record 126:617, 1990
33a. Grounds RM, Twigley AJ, Carli F, et al. The hemodynamic effects of intravenous induction. Comparisons of the effects of thiopentone and propofol. Anesthesia 40:735, 1985
34. Sebel PS, Lowdon JD. Propofol: A new intravenous anesthetic. Anesthesiology 71:260, 1989
35. Azari DM, Cork RC. Comparative myocardial depressive effects of propofol and thiopental. Anesth Analg 77:324, 1993
36. Park WK, Lynch C. Propofol and thiopental depression of myocardial contractility: A comparative study of mechanical and electrophysiologic effects in isolated guinea pig ventricular muscle. Anesth Analg 74:395, 1992
36a. Bufalari A, Miller SM, Giannoni C, et al. The use of propofol as an induction agent for halothane and isoflurane anesthesia in dogs. J Am Anim Hosp Assoc 34:84, 1998
37. Ilkiw JE, Pascoe PJ, Haskins SC, et al. Cardiovascular and respiratory effects of propofol administration in hypovolemic dogs. Am J Vet Res 53:2323, 1992
37a. Muir WW III, Gadawski JE. Respiratory depression and apnea induced by propofol in dogs. Am J Vet Res 59:157, 1998
38. Hickey RF, Eger EI. Circulatory effects of inhaled anaesthetics. *In* Prys-Roberts C (ed): The Circulation in Anaesthesia. London, Blackwell Scientific Publications, 1980, p 441
39. Steffey EP. Inhalation anesthetics. *In* Thurmon JC, Tranquilli WJ, Benson GJ (eds): Lumb & Jones Veterinary Anesthesia. 3rd ed. Baltimore, Williams & Wilkins, 1996, p 297
39a. Hodgson DS, Dunlop CI, Chapman PL, et al. Cardiopulmonary effects of anesthesia induced and maintained with isoflurane in cats. Am J Vet Res 59:182, 1998
40. Bednarski RM, Muir WW. Arrhythmogenicity of dopamine, dobutamine and epinephrine in thiamylal, halothane anesthetized dogs. Am J Vet Res 44:2341, 1983
41. Bovill JG, Sebel PS, Stanley TH. Opioid analgesics in anesthesia: With special reference to their use in cardiovascular anesthesia. Anesthesiology 61:731, 1984
42. Savarese JJ, Philbin DM. Cardiovascular effects of neuromuscular blocking agents. Int Anesthesiol Clin 17:13, 1979
43. Philbin DM, Hutter AM Jr. Intraoperative cardiac arrhythmias. Int Anesthesiol Clin 17:55, 1979
44. Osborne CA, Polzin DJ. Azotemia: A review of what's old and what's new. Part II. Localization. Compend Cont Educ Pract Vet 5:561, 1983
45. Kelman GR. Interpretation of CVP measurements. Anaesthesia 26:209, 1971
46. Haskins SC. Shock. *In* Kirk RW (ed): Current Veterinary Therapy. Vol VIII. Philadelphia, WB Saunders, 1983, p 2
47. Cullen DJ. Interpretation of blood-pressure measurements in anesthesia. Anesthesiology 40:6, 1974
48. Meldrum SJ. The principles underlying Dinamap-A microprocessor-based instrument for the automatic determination of mean arterial pressure. J Med Eng Technol 2:243, 1978
49. Kittleson MD, Olivier NB. Measurement of systemic arterial blood pressure. Vet Clin North Am 13:321, 1983
50. Klevans LR, Hirhaler G, Kovacs JL. Indirect blood pressure determination by Doppler technique in renal hypertensive cats. Am J Physiol 237:H720, 1979
51. Morgan RV. Systemic hypertension in four cats. Ocular and medical findings. J Am Anim Hosp Assoc 22:615, 1986
52. Shapiro BA, Harrison RA, Walton JR. Clinical Application of Blood Gases. 3rd ed. Chicago, Year Book Medical Publishers, 1982, p 77
53. Clark JS, Votteri B, Arigno RL, et al. Noninvasive assessment of blood gases. Am Rev Respir Dis 145:220, 1992

39

Basic Cardiovascular Surgery and Procedures

GEORGE E. EYSTER

PREREQUISITES FOR SUCCESSFUL INTERVENTION

Successful outcome of cardiovascular surgery requires accurate diagnosis, thorough understanding of anatomy and physiology, medical management to control or correct cardiovascular compromise or serious arrhythmias, technical surgical skill and experience, and good anesthesia support.[1, 2] Congenital heart diseases are reviewed in detail with respect to clinical characteristics, diagnostic features, and therapy (chapter 24). The epidemiology and prevalence of cardiovascular diseases are discussed in chapter 23. Anesthetic considerations (chapter 38) and anatomy (chapters 1 and 2) have been thoroughly reviewed. Additional information concerning diagnostic, pathophysiologic, and therapeutic aspects of cardiovascular diseases is contained elsewhere in this book.

CARDIOVASCULAR SURGERY

Surgical intervention remains the preferred treatment for many congenital and acquired cardiac diseases. Surgery may offer palliative but stabilizing results in some disorders; in others, anatomic repair and hemodynamic resolution can be accomplished. Principles of good surgical technique (e.g., hemostasis, atraumatic tissue handling, secure knot tying) must be combined with specialized technical skills to perform closed cardiac procedures or open heart surgery. The latter requires venous inflow occlusion (<4 minutes) to allow short procedures to be performed, or cardiopulmonary bypass to support longer operative techniques. Patient monitoring and postoperative supportive care are essential for successful surgery.

INTERVENTIONAL CATHETERIZATION

Interventional cardiac catheterization is gaining popularity for treating certain cardiovascular conditions (see chapters 9 and 24). The most common

applications include balloon dilation (valvuloplasty) of stenotic pulmonic and aortic valves[3–5] and transcatheter techniques to close patent ductus arteriosus.[6–8] The use of special "snare" catheters to retrieve iatrogenic cardiovascular foreign bodies in animals can obviate thoracotomy and cardiotomy in some cases.[9, 10] The importance of clinical diagnosis and therapy is the same as described above.

PATIENT MONITORING

Evaluation of ventilation is critical during and after surgery. Arterial CO_2 tension ($PaCO_2$) is a good measure of alveolar ventilation. Hypoventilation is indicated by a $PaCO_2$ greater than 40 mmHg. Other blood gas determinants such as arterial oxygen tension [PaO_2] (maintaining $PaO_2 > 80$ mmHg) are also informative. Monitoring cardiac electrical activity (ECG) for heart rate, arrhythmias, and P-QRS-T morphology is mandatory. Also recommended is arterial blood pressure monitoring (maintain systolic pressure > 90 mmHg and mean blood pressure > 65 mmHg) and pulse oximetry monitoring (maintain hemoglobin oxygen saturation [SaO_2] > 90%). A simple central venous pressure system is frequently helpful (maintain between 5 and 10 cm H_2O), particularly in right-sided heart disease.

During open chest procedures, one may visually observe and directly palpate cardiovascular and pulmonary structures. The lungs are assessed for appropriate expansion in response to positive-pressure ventilation. The pericardial sac is examined for pericardial effusion. The pink appearance of the myocardium, particularly the left atrium, suggests good ventilation and adequate oxygenation. When cyanosis or hypoventilation is present, the myocardium appears darker (preceding ECG or blood pressure abnormalities). An approximation of arterial blood pressure is determined by palpating the aortic arch or descending aorta. As a rough rule of thumb: (1) application of digital aortic pressure should cause the aorta to move away from the pressure point if the arterial pressure is greater than 110 mmHg; (2) if the vessel wall indents and the whole artery moves as it is pressed, pressure is approximately 80 to 110 mmHg; (3) if, with digital pressure, the artery indents easily and partially occludes before it is moved, arterial pressure is less than 80 mmHg, and the animal is too deeply anesthetized or is in a low cardiac output state.

Bradycardia accompanies an excessively deep anesthetic plane and should be avoided. Administration of atropine (0.03 to 0.04 mg/kg) or glycopyrrolate (0.01 to 0.015 mg/kg) SC or IM reduces difficult-to-manage bradyarrhythmias. This is particularly important in patients requiring manipulation of the cardiac base (e.g., with patent ductus arteriosus surgery), since vagal nerve stimulation induces bradycardia unless a vagolytic drug is used.

SURGICAL APPROACHES AND TECHNIQUES

PERICARDIOCENTESIS

Pericardial effusion is easily diagnosed by echocardiography (chapter 8). Pericardiocentesis may be indicated to obtain fluid for diagnostic purposes, as when infectious pericarditis or neoplastic effusion is suspected, or to relieve intrapericardial pressure in cases of cardiac tamponade. This technique is described in detail in chapter 29.

MEDIAN STERNOTOMY

ADVANTAGES. Median sternotomy has several advantages over a lateral thoracotomy: (1) visualization of both sides of the thorax, (2) proximity to the right ventricular outflow tract, (3) visualization of all heart chambers, and (4) reduced hemorrhage for some procedures requiring heparin therapy. Bilateral partial lobectomy is easily performed, but complete lobectomy is often difficult. The caudal vena cava, main pulmonary artery, and both sides of the heart can be manipulated.

DISADVANTAGES. A major disadvantage of median sternotomy is delayed healing if pleural effusion continues postoperatively. Because of the patient's preference for sternal positioning, the pleural effusion will seep into the surgical site. This will delay and occasionally inhibit healing.

SURGICAL TECHNIQUES

Median sternotomy is popular in humans but has not been used extensively in the dog or cat. It is an ideal technique for certain procedures that include cardiac tumor removal, right ventriculotomy, pericardiectomy, and exploratory surgery. This approach to the heart can be accomplished by placing the animal in dorsal recumbency and incising the skin from just cranial to the manubrium to just caudal to the xiphoid. The procedure need not extend along the full length of the sternum unless wide exposure of the thorax is required. The approach to the cranial heart and anterior mediastinum may require the median sternotomy only from the manubrium to the midsternal area, whereas most procedures on the heart may be accomplished with incisions only in the posterior two thirds

of the sternum. By opening only a portion of the sternum, closure is simplified, healing is facilitated, and patient postoperative pain is greatly reduced. The incision is made strictly on the midline (avoiding the need to transect muscles) and continues between the pectoral muscles to the sternebrae. The sternebrae are divided by saw, chisel, or heavy scissors. Closure usually requires wiring the sternebrae. At least three layers of tissue are then closed. Healing is facilitated if the sternebrae have not been cut from manubrium to xiphoid, so that several sternebrae may be left to stabilize the sternum.

LATERAL THORACOTOMY

ADVANTAGES. Most cardiovascular procedures are performed using a left lateral thoracotomy at the 4th intercostal space. This approach is adequate for most clinical conditions requiring surgical intervention in the heart and great vessels. It allows exposure to the right ventricular outflow tract and main pulmonary artery and the ductus arteriosus. The basic thoracotomy technique can be applied for thoracotomies at other intercostal spaces. A right intercostal thoracotomy allows exposure of the right auricle, atrium, and ventricle; cranial and caudal vena cavae; azygos vein; and right lung lobes.

DISADVANTAGES. With a dedicated (e.g., left 4th intercostal) thoracotomy approach, visualization of structures lying on both sides of the thorax is not possible. Proximity to the right ventricular outflow tract and visualization of all heart chambers are less than with a median sternotomy.

SURGICAL TECHNIQUES

With the animal in right lateral recumbency, the left 4th intercostal space is identified at the posterior border of the scapula. The skin incision is made from the level of the ventral portion of the vertebrae to just proximal to the ventral midline of the animal. The cutaneous trunci and subcutaneous tissues are then divided, using scissors; most thoracotomy bleeding will occur at this layer. The latissimus dorsi muscle is the first major structure to be cut and is partially transected from its ventral border, approximately halfway to its dorsal border. The latissimus dorsi does not need to be transected but requires constant dorsal retraction throughout the procedure if the partial transection is not performed. The scalenus muscle inserts as an aponeurosis beginning at the 5th rib. The fibrous aponeurosis should be transected and the scalenus reflected anteriorly. At this point, the intercostal space should be verified by palpating beneath the latissimus dorsi to the thoracic inlet and counting the ribs. In extremely small animals, a curved hemostat may be passed to the thoracic inlet and reflected off each rib to identify the fourth intercostal space. The serratus ventralis muscle is divided between its heads at the appropriate rib space. The fascia and connective tissue are then divided over the 4th intercostal space, revealing the intercostal muscles. External and internal intercostal muscles are divided in the posterior one third of the rib space, thereby protecting the intercostal artery, vein, and nerve. The pleura is then visualized.

The anesthesiologist should permit the lungs to collapse as a small hole is surgically made in the pleura. The pleural incision is than extended dorsally and ventrally (Fig. 39–1). At the ventral end of the incision, care should be taken not to interrupt the internal thoracic artery as it courses within 1 cm of the lateral border of the sternum. Rib retractors are then placed. To complete the lateral thoracotomy, the left anterior lung is rotated at its base and packed posteriorly.

SURGICAL PROCEDURES FOR CARDIOVASCULAR DISEASE

PULMONIC STENOSIS

Pulmonic stenosis (PS) represents congenital narrowing of the pulmonic valve, right ventricular outflow tract, or pulmonary artery. In the dog, valvular PS is the most common form. Muscular infundibular PS may occur singularly or secondary to any of the other types. Supravalvular or peripheral pulmonary artery PS is rare. Pulmonary valve dysplasia may present as a malformed valve, including the immediate subvalvular tissue, although isolated subvalvular PS is rare. Preoperative considerations require careful characterization of the anatomic type, location, and severity (see chapters 8, 9, and 24).

Cardiac catheterization has been the gold standard for diagnostic confirmation and localization, and to gauge severity of the stenotic lesion. At the time of catheterization, a balloon dilation can also be considered to attempt a primary "repair," or to provide some clinical improvement and retard progression until the animal grows and other surgical approaches can be used.[4] Balloon valvuloplasty usually provides an excellent outcome when PS is caused by fusion of pulmonary valve leaflets. Surgery is generally reserved for cases of PS caused by fibromuscular lesions, severe dysplasia, or pulmonary valve hypoplasia (chapters 9 and 24). Based upon catheterization-derived pressure recordings, guidelines to grade the severity of PS are as follows:

(1) No intervention (surgery or balloon valvuloplasty) is recommended when right ventricular systolic pressures are less than 70 mmHg, or when gradients across the obstruction are less than 50 mmHg;

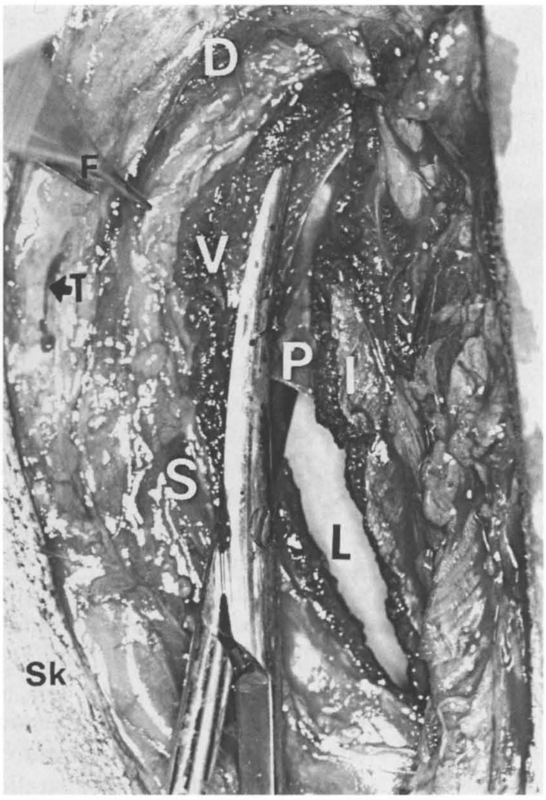


FIGURE 39–1

Left lateral thoracotomy at the 4th intercostal space. Craniad is to the left. Visible, from left to right, are skin *(Sk)*, cutaneous trunci *(T)*, latissimus dorsi *(D)* at the forceps *(F)*, the anteriorly reflected scalenus *(S)*, serratus ventralis *(V)*, and the intercostal muscles *(I)*. The pleura *(P)* is being cut and the lung *(L)* is seen through the thoracic opening.

(2) Intervention is probably indicated when right ventricular (RV) pressures of 70 to 120 mmHg or gradients of 50 to 100 mmHg are present;
(3) Intervention is invariably indicated with RV pressure greater than 120 mmHg and gradients greater than 100 mmHg.

When low-to-medium pressures are recorded in mature animals with PS, intervention is usually not required. However, when similar pressures are recorded in growing dogs with PS, it is anticipated that the disease will become more severe and that the animal will become a candidate for intervention.

It is important to recognize that anesthesia significantly depresses pressure gradients up to 50 percent compared with those measured by Doppler echocardiography in the awake dog. Therefore, many cardiologists prefer gradient measurements generated by Doppler echocardiography (see chapter 24).

BISTOURY TECHNIQUE

Indications and Contraindications

This technique is indicated for valvular PS. It is of no advantage for supravalvar or muscular PS and has little value in subvalvar PS or cases of severely dysplastic pulmonary valves. A serious disadvantage of bistoury repair for muscular PS is lack of visualization of the obstructed area. However, it is a relatively simple technique to perform and has been used in veterinary medicine since 1953.[11, 12]

Surgical Techniques

The value of this procedure is related to its simplicity. Either a left lateral thoracotomy in the 4th intercostal space or median sternotomy provides surgical access. The right ventricular outflow tract is visualized and a pursestring suture placed in this relatively avascular region. A stab incision is made into the right ventricle, a bistoury (frequently a teat bistoury) is introduced into the right ventricular outflow tract across the stenotic valve, and several cuts are made in the valve (Fig. 39–2). The bistoury is then removed, the pursestring is tightened down, and the chest is closed routinely. This technique requires minimal aftercare, and the immediate results are generally excellent in pure valvular PS.

MODIFIED BROCK PROCEDURE

Indications and Contraindications

This simple technique is used effectively only for solitary muscular or infundibular PS. It is of no value

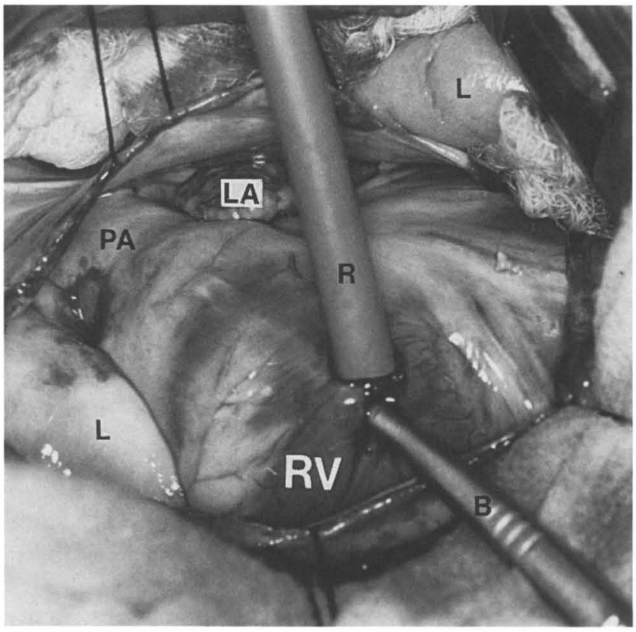


FIGURE 39–2

Left lateral thoracotomy at the 4th intercostal space. A bistoury *(B)*, introduced through a pursestring suture in a Rumel tourniquet *(R)* to control bleeding, has been advanced into the right ventricle *(RV)*. It is passed through the obstruction, where cuts are then made in the muscular or fibrous subvalvar ring. *L*, lung; *PA*, pulmonary artery; *LA*, left auricle.

for the other types of PS. The major disadvantage of this procedure lies in the inability to visualize the right ventricular myocardium being surgically excised.

Surgical Techniques

This procedure resembles the bistoury technique except that the instrument introduced into the right ventricular outflow tract is an infundibular rongeur. The offending tissue is excised with this instrument. Chest closure and postoperative management are identical to that of the bistoury technique.[12]

VALVULOTOME VALVOTOMY

Indications and Contraindications

Valvulotome valvotomy for PS is a moderately complicated technique that may be effective in valvular, subvalvular, and dysplastic PS. Its disadvantages include lack of visualization of the offending right ventricular myocardium as the valvulotome cuts are made. However, when patients are appropriately selected, valvotomy using a valvulotome may be very effective.

Surgical Techniques

Valve dilation using a valvulotome is similar to the previously described techniques. In using a valvulotome, both valvular and fibrous subvalvular stenoses and most dysplastic pulmonary valve obstructions can be opened. The technique is identical to the previously described procedures; however, in this case the valvulotome is introduced into the right ventricle and is passed into the obstructed area. As the valvulotome is then opened, cuts are made in either the valve, subvalvular tissue, or both. Closure and postoperative management are identical to the previously described techniques.

INFLOW OCCLUSION AND PULMONARY ARTERIOTOMY

Indications and Contraindications

Pulmonary arteriotomy is effective in valvular subvalvar and dysplastic valves. It is not effective in muscular infundibular stenosis, nor is it effective in supravalvar PS. The technique has the significant advantage of permitting visualization of the offending obstructive tissue. Disadvantages of inflow occlusion for PS are (1) the slightly more difficult surgical technique, and (2) the fact that in immature animals the fibrosis associated with the surgery will become permanent. This technique is therefore not recommended in animals younger than 6 months of age.

Surgical Technique

Inflow occlusion and pulmonary arteriotomy (Swan procedure) is perhaps the most efficient technique for PS caused by valvular, immediate subvalvar, or pulmonary valve dysplasia lesions.[13] Although induction of mild hypothermia is part of this technique when used for humans, this is not necessary in dogs.

The inflow occlusion pulmonary arteriotomy repair for PS is accomplished through a left lateral thoracotomy in the 4th intercostal space. The lungs are reflected and umbilical tapes placed around the cranial and caudal vena cava. The cranial vena cava is identified by careful blunt dissection. It is located cranial to the heart and ventral to the brachycephalic artery. Once the vena cava is identified, umbilical tape is passed around the vessel, and a Rumel tourniquet is loosely positioned over the umbilical tape. The caudal vena cava is poorly identified from a 4th intercostal space, requiring that the heart be rotated cranially. This necessitates breaking down the mediastinum caudal to the heart.

Once the caudal vena cava is visualized, a tourniquet is placed around it similar to that of the anterior cava. The pericardium is then opened dorsal and parallel to the phrenic nerve. Pericardial basket sutures are placed on both edges of the cut pericardium, and the heart is elevated using the basket sutures. The pulmonary artery is identified, and a double row of 4-0 vascular stay sutures is placed in the poststenotic dilatation, or slightly toward the heart from the poststenotic dilation. The animal must be well ventilated, and the Rumel tourniquets are tightened to occlude the vena cava.

Approximately 15 seconds are required for the right side of the heart to empty, and an incision is then made in the pulmonary artery between the stay sutures. The pulmonary artery is opened (Fig. 39–3), suction is applied to permit visualization, and the stenotic pulmonary valve or subvalvular tissue is incised and/or removed by scalpel, scissors, or valve dilator. The valve is reformed to approximate a normal valve or it is excised, depending on the type of disease. The stay sutures are then elevated, a partially occluding clamp (Satinsky) is placed on the pulmonary artery closing the opening, and the tourniquets are removed from the vena cava to re-establish the circulation.

Throughout the occlusion procedure, some hemorrhage will occur, since the azygos vein and coronary sinus blood flow continues, necessitating the need for suction. The occlusion time should be confined to less than 3 minutes, preferably less than 2 minutes, which is almost always adequate to accomplish the repair; if more time is needed, a second occlusion can be initiated after a 5-minute recovery.

After circulation is re-established, the pulmonary artery is closed with a 4-0 continuous suture pattern.

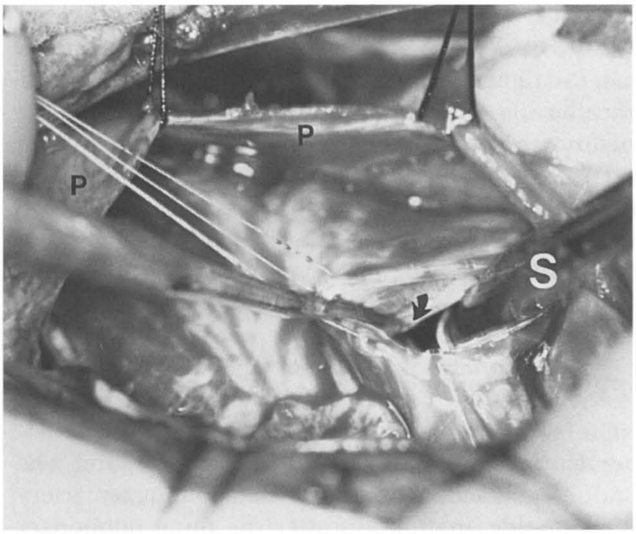


FIGURE 39–3

Left lateral thoracotomy at the 4th intercostal space. The lungs are reflected to expose the heart. Elevation of the heart is facilitated by pericardial basket sutures. Vascular stay sutures are placed in the poststenotic dilation. The pulmonary artery is opened. Suction *(S)* is used to remove blood from the surgical field as the stenotic pulmonary valve is incised *(arrow)* with a #11 scalpel blade. P, pericardium.

Closure and postoperative management are routine. Patients tend to have a slight, 1- to 2-hour delay in anesthetic recovery, which is probably associated with the short period of anoxia sustained during the inflow occlusion.

PATCH-GRAFT TECHNIQUE

Indications and Contraindications

The greatest advantage of this method is that it permits expansion and decompression of the right ventricular chamber. Also, the patch can be made very large to facilitate growth in the young patient with severe PS, which would otherwise require multiple operations. Disadvantages are related to the difficulty of entering the right ventricular lumen when severe hypertrophy is present, the brutal manipulation involved in cutting the right ventricle, and the difficulty in some cases of cutting through the fibrous, thickened PS with the cutting wire. An anomalous left coronary artery (originating from a single right coronary artery) that encircles the stenotic right ventricular outlet and valve is an absolute contraindication (see Fig. 24–3).[14]

Surgical Procedures

The patch-graft technique is an effective procedure for relieving valvular and subvalvular dysplastic valves and muscular PS.[15] This was first performed with a cutting wire positioned under a patch in such a way that when the wire is pulled, the ventricular wall is cut, opening the ventricle and pulmonary artery to the patch. However, in severe PS, particularly with right ventricular hypertrophy and dysplastic or very fibrous valves, the procedure may be difficult to perform successfully.

This technique is accomplished through a left lateral thoracotomy in the 4th intercostal space or by median sternotomy. The right ventricular outflow tract to the pulmonary valve is identified. A cutting wire is placed into the ventricle and pushed out the main pulmonary artery. This approach is facilitated by passing the wire through an over-the-needle catheter (a small urinary catheter or large 14- to 16-gauge over-the-needle injection catheter can be used). The difficulty of identifying the ventricular chamber enclosed within the hypertrophied right ventricular wall is obviated when the catheter penetrates the ventricular chamber and blood flows through the catheter. The ventricular chamber is thus identified, the catheter is passed into the pulmonary artery, and a stylet is placed into the catheter. This stylet facilitates the catheter exiting from the pulmonary artery through the arterial wall. A Gigli wire is passed through the catheter, and the catheter is withdrawn. A small (6-0) pursestring suture is placed in the pulmonary artery around the catheter at its point of exit to eliminate bleeding while the patch is being sutured into place. A Dacron, Gore-Tex, or pericardial patch is then placed over the wire from the pulmonary artery to the right ventricle. It is secured by continuous suture, with the last one or two sutures not drawn down (Fig. 39–4). When the patch is in

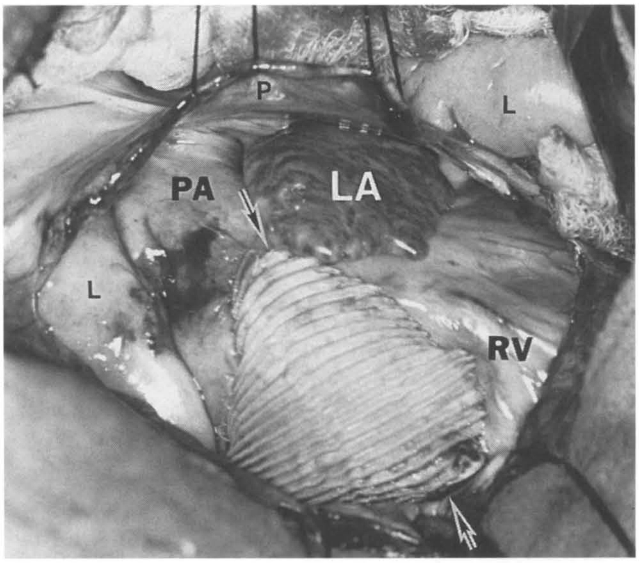


FIGURE 39–4

Left lateral thoracotomy at the 4th intercostal space. The lungs *(L)* are reflected. The pericardium *(P)* is incised parallel and ventral to the phrenic nerve. Pericardial basket sutures are placed to assist in elevating the heart. A patch-graft of woven Dacron is in place from the pulmonary artery *(top arrow)* to the body of the right ventricle *(bottom arrow)*. *PA,* pulmonary artery; *LA,* left auricle; *RV,* right ventricle.

place, the cutting wire is then pulled out, and the right ventricle, proximal pulmonary artery, and obstructed area of pulmonic stenosis are opened into the patch. Digital pressure controls the bleeding at the last two sutures as the wire is removed at the ventral portion of the patch. These last sutures are then secured.

A chest drain tube should be placed and remain for 24 hours postoperatively. If pleural effusion develops as a result of foreign material (e.g., Dacron), it is manually evacuated. The chest drain tube is removed approximately 12 hours after pleural effusion abates. We prefer to place animals undergoing patch-graft technique with foreign material on preoperative antibiotics that are continued for 1 week after surgery. Once the chest drain tube is removed, patient management is similar to the previously described techniques.

If a patch-graft is to be used to include the right ventricular outflow tract and pulmonary artery, then the normal coronary artery anatomy must be validated preoperatively by left-sided cardiac catheterization and coronary arteriography. This procedure must not be used in dogs in which an aberrant coronary artery courses below the main pulmonary artery (see Fig. 24–3).[14]

ORTON MODIFICATION. This modification combines a form of inflow occlusion and patch-graft technique in which no cutting wire is used.[16] Bleeding and trauma to the right ventricular wall are markedly reduced. In this technique, after placing an overlarge patch-graft a double row of stay sutures is inserted in the graft, and the graft is then cut between the stay sutures. Inflow occlusion is instituted as noted earlier, and the right ventricle to pulmonary artery cut is made with scalpel or scissors directly into those tissues with direct visualization. The right ventricle, stenotic valve area, and proximal pulmonary artery are cut and opened into the patch. Direct visualization of the opening into the patch is thereby permitted, which eliminates the risk associated with the occasional unwanted tear by the cutting suture. This modification has become our preferred patch-graft technique since it eliminates the bleeding during patch placement and difficulty of placing the wire in the lumen.

CONDUIT REPAIR

Indications and Contraindications

Although a variety of PS lesions can be repaired by conduits, this technique has not met early expectations. Perhaps the best indication for conduit repair is for supravalvular PS since it preserves the normal pulmonic valve. Here, a conduit can be inserted from the proximal pulmonary artery to the distal pulmonary artery around the obstruction.[17] In some types of severe dysplasia, conduits from the right ventricle to the pulmonary artery can be useful to bypass the obstruction. In rare cases of tricuspid valve atresia, conduits from the right atrium to the pulmonary artery (Fontan procedure) can bypass the obstruction. To date, the only successful use of conduits in veterinary medicine has been from proximal pulmonary artery to distal pulmonary artery or from the right ventricle to the pulmonary artery. Because of the many problems associated with conduits, these procedures are recommended only for supravalvar PS.

Surgical Technique

The surgical procedure is accomplished by a left lateral thoracotomy in the 4th intercostal space. The conduit is attached distally to the pulmonary artery by end-to-side anastomosis after the distal pulmonary artery has been partially occluded. The proximal attachment of the conduit is identical to the attachment distally.

OPEN HEART SURGERY

Open heart surgery is effective for all types of PS but has a higher mortality rate. Since the closed techniques described are effective, safe, and more cost effective, open heart surgery for PS repair cannot be recommended for clinical practice at this time.

AORTIC STENOSIS

Aortic stenosis represents a congenital narrowing of the left ventricular outflow tract (subvalvular), aortic valve (valvular), or aorta (supravalvular). Subvalvular aortic stenosis (SAS) is the predominant lesion in dogs. Aortic stenosis is rare in cats.

Indications and Contraindications

The severity of aortic stenosis based upon cardiac catheterization is considered by our laboratory as follows:

(1) *Mild* with gradients across the aortic valve of less than 50 mmHg,
(2) *Moderate* when gradients are 50 to 90 mmHg, or
(3) *Severe* with gradients of greater than 90 mmHg.

In humans, critical aortic stenosis is present when gradients exceed 100 mmHg. Adult dogs with mildly elevated gradients tend to remain asymptomatic (median survival, 50.1 months), whereas those with severe gradients (> 80 mmHg) have a greatly increased risk of death within 3 years (median survival, 18.9 months).[18] Thus, surgical intervention should be attempted only with severe aortic stenosis, since perioperative mortality and morbidity are relatively high. In the symptom-

atic growing dog, surgery should be accomplished before severe left ventricular hypertrophy occurs.

Clear predictions of long-term outcomes associated with interventional techniques will require further study. Long-term data of valve dilation using balloon valvulotomy and valvulotome techniques are just now becoming available and require further study. In contrast, studies following left ventricular to aortic conduit repair are not available. Long-term results (at least 10 years) with open heart surgical techniques are variable. Although some dogs have done well, approximately half have developed congestive cardiomyopathy at 5 to 7 years of age. Whether this is related to cardioplegia used during surgery, disease-related myocardial injury that preceded surgery, or to other factors is unknown.

VALVE CONDUITS

Surgical Technique

Valved left ventricular apical-aortic conduits have been used for the past decade[19] to treat aortic stenosis in the dog. The conduit is attached proximally to the apex of the left ventricle and to the descending aorta distally. The device permits decompression of the left ventricle and provides an alternative exit for blood from the left ventricle, reducing the critical hypertrophy that occurs with the disease. A valve in the conduit protects against aortic regurgitation. However, results have been variable. The cost of valve conduits is high, and the requirement for anticoagulation is complicated. Consequently, these conduits cannot be advocated currently for veterinary patients.

OPEN HEART SURGICAL RESECTION

Surgical Techniques

Open resection of the subvalvular fibrous ring during cardiopulmonary bypass has been described in dogs.[20, 21] In addition, ventricular septal myectomy may be performed at the same time on the obstructing fibromuscular tissue beneath the aortic valve, depending on the degree of hypertrophy and outflow tract obstruction. In successful cases, the gradient has been reduced both at surgery and 1 year postoperatively.[21] Patients with isolated, discrete subvalvular rings may be more successfully corrected than those with complicated or tunnel-like lesions. Although this technique appears to be effective, the intraoperative mortality (10 to 20 percent), plus the cost of open heart surgery, has limited the availability of this procedure. Successful postoperative reduction in the left ventricular outflow gradient does not eliminate the risk of sudden death.

VALVE DILATION

Surgical Technique

Valve dilation can be accomplished using percutaneous balloon valvuloplasty (see chapters 9 and 24) introduced through the femoral or carotid artery and directed under fluoroscopic guidance through the aortic valve. Favorable short-term results have been reported,[5] but long-term follow-up is often disappointing,[22] with transvalvular gradients often increasing back to pre-interventional levels.

Surgical closed transventricular valve dilation of the fibrous, subvalvular aortic ring, using a valve dilator, has been described.[23] The procedure is best accomplished via a median sternotomy, but it can be done with difficulty through a left lateral thoracotomy at the 5th intercostal space. The apex of the left ventricle is identified, and a large, deep, double pursestring suture is placed there. A stab incision is then made into the left ventricular cavity, and the valvulotome is introduced into the left ventricle. The left index finger is placed around the base of the heart at the aortic valve to act as a guide to direct the valvulotome toward the aortic valve. When the tip of the valvulotome is palpated in the aorta, the valvulotome is pulled back through the aortic valve and opened, and the obstructing lesion is cut. Multiple cuts are then made as the valvulotome is retracted through the subvalvar area, incising the obstructive ring. When the valvulotome can be opened fully and the subvalvar area dilated, the valvulotome is removed from the left ventricle and the pursestring suture is tied. Closure is routine. Results of surgery using the valvulotome appear to be good to date, with survival exceeding 80 percent. Postoperative management is uncomplicated, requiring 72 hours for observation and management of arrhythmias. Results of 5-year follow-up are favorable.

ATRIAL SEPTAL DEFECTS

Atrial septal defects are uncommon. Ostium primum defects are generally large and may contribute to complex atrioventricular septal defects or endocardial cushion defects, especially in felines (see chapter 24). These lesions cause volume overload resulting in congestive heart failure.[24] Although rare in the dog, this lesion is usually significant when encountered and should be repaired.[25-26a] In contrast, solitary ostium secundum atrial septal defects rarely cause significant volume overload. For those lesions that warrant surgery, cardiopulmonary bypass is required; the right atrium is opened and secundum defects are closed either by primary suture or by patch, depending on the defect size. Ostium primum defects require patch repair.[27]

VENTRICULAR SEPTAL DEFECTS

Ventricular septal defects (VSDs) result from failure or incomplete development of the membranous or muscular interventricular septum. Most VSDs are located high in the membranous septum, although atrioventricular septal defects occur infrequently.[24, 28] The majority of VSDs are small, restrictive, and generally asymptomatic. More advanced, larger, or complex lesions may require surgical intervention.

PULMONARY ARTERY BANDING

Indications and Contraindications

Definitive treatment of symptomatic animals requires open heart surgery using cardiopulmonary bypass,[29] but this carries a high risk and is expensive. Deep hypothermic circulatory arrest[30] is curative, is extremely time consuming, carries an even higher risk, and requires extensive training. Pulmonary artery banding is palliative, is relatively simple, and has a very low risk, but it cannot be performed in immature animals.[31, 32] It is the preferred technique in mature patients. This technique creates a supravalvular PS that increases right ventricular pressures, thereby diminishing the severity of left-to-right shunting through the VSD. If excessive banding increases RV pressures too much, right-to-left shunting and cyanosis will result.

Surgical Techniques

Surgery is performed through a left lateral thoracotomy in the 4th intercostal space. By careful blunt dissection using a right-angle forceps, the main pulmonary artery is separated from the aorta on the medial side. Inadvertent tearing of the right pulmonary artery is less likely to occur when careful dissection is performed around the artery from a cranial to caudal direction. The dissection should be carried out close to the heart since the main pulmonary artery in the dog is quite short.

After the instrument has circled behind the main pulmonary artery, umbilical tape is passed around the vessel. The pulmonary artery can then be compressed with the umbilical tape until the pulmonary artery is one third its original diameter or, if distended, one third the apparent diameter at the pulmonary valve (Fig. 39–5). The umbilical tape is then sutured at that position to maintain the pulmonary artery at the one-third-normal diameter. If desired, a knot can then be placed in the umbilical tape. Pulmonary artery size should decrease, and the color of the pulmonary artery should darken with reduction of the shunt.

If the band is placed too loosely, right ventricular pressure will not be elevated sufficiently to reduce shunt flow from the left ventricle. If the band is placed too tightly, potential right-to-left shunting through the VSD can produce severe cyanotic heart disease. The pulmonary artery pressure should be reduced by one half and the right ventricle pressure increased to twice the prebanding pressure. These pressures can be measured by a small needle inserted directly into the pulmonary artery distal to the band or into the right ventricular lumen.

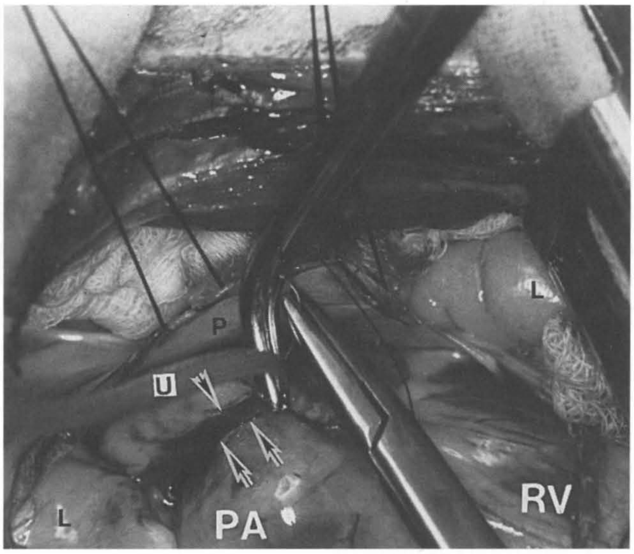


FIGURE 39–5

Left lateral thoracotomy at the fourth intercostal space. The lungs *(L)* are reflected, and the pericardium is incised parallel and dorsal to the phrenic nerve. Pericardial basket sutures assist in elevating the heart. An umbilical tape is positioned around the pulmonary artery *(arrows),* tightened, and held in position with right-angle forceps. The pulmonary artery diameter is reduced to one third the diameter of the pulmonary artery at its origin, the pulmonary valve annulus. Sutures are then placed (e.g., needle holder) and tied in the umbilical tape to maintain this tape diameter. *P,* pericardium; *PA,* pulmonary artery (labeled at the approximate level of the pulmonary valve annulus); *RV,* right ventricle.

Closure and postoperative management are routine. Animals with pulmonary artery banding recover quickly and should be monitored for a week to 10 days for cyanosis. If cyanosis occurs, right-to-left shunting has developed and the band must be removed or loosened. With successful surgery, animals may have normal longevity, albeit with reduced activity in some instances. In the dog this technique has produced effective results in excess of 10 years.

TETRALOGY OF FALLOT

This complex congenital defect is composed of four components: (1) pulmonic stenosis (right ventricular outflow obstruction), (2) secondary right ventricular hypertrophy, (3) high ventricular septal defect, and (4) overriding (dextropositioned) aorta. Some pets will tolerate this condition for years with medical management.

Indications and Contraindications

Surgical treatment should be instituted only when medical therapy fails. Surgical palliation or correction can be considered. Although some cases have been corrected by open heart surgery using cardiopulmonary bypass,[32a] the procedure is costly and carries a high mortality. Palliative procedures using systemic to pulmonary artery shunts appear to be effective and are advocated when medical therapy fails. These shunts include the classic Blalock-Taussig anastomosis, Pott's anastomosis, or graft or conduit connections.[33, 34]

BLALOCK ANASTOMOSIS

Surgical Techniques

The purpose of shunt surgery is to return a large portion of the partially oxygenated systemic blood to the lung, to then be oxygenated and returned to the left side of the heart. The Blalock anastomosis has been used successfully in humans since 1947, first as a final repair, and currently as a palliative technique.

Blalock anastomosis is accomplished through a left thoracotomy at the 4th intercostal space. The darkened pulmonary artery can be visualized. The left subclavian artery is identified, ligated as far distally as possible, clamped using a bulldog clamp, and transected distally. The left subclavian artery is then mobilized toward the pulmonary artery. If no kinking develops at the origin of the left subclavian artery, a direct end-to-side anastomosis of the left subclavian to pulmonary artery can be accomplished. The pulmonary artery is partially occluded with a Satinsky-type clamp, and the anastomosis is completed using a continuous suture pattern. The pulmonary artery clamp is removed, the suture holes are allowed to fill with blood, and 1 or 2 minutes later the subclavian artery clamp can be removed (Fig. 39–6).

If the animal is small, or if the left subclavian artery kinks at the origin from the aorta when rotated toward the pulmonary artery, a revision of the left subclavian artery origin should be considered. The aorta should be clamped with a partially occluding clamp at the point where the subclavian artery exits. A diamond-shaped incision, partially including the aorta and partially including the left subclavian artery, can be made at the junction of the subclavian artery and aorta. The subclavian artery is then rotated toward the pulmonary artery and the two angles of the diamond are sutured together. This makes a more direct outflow from the aorta to the left subclavian artery and removes the shelf of tissue produced by the kinking of the vessel as it is rotated ventrally and posteriorly. The final portion of the anastomosis to the pulmonary artery is carried out in routine manner. An alternative operation is to extend the length of the short subclavian artery with a Gore-Tex conduit.

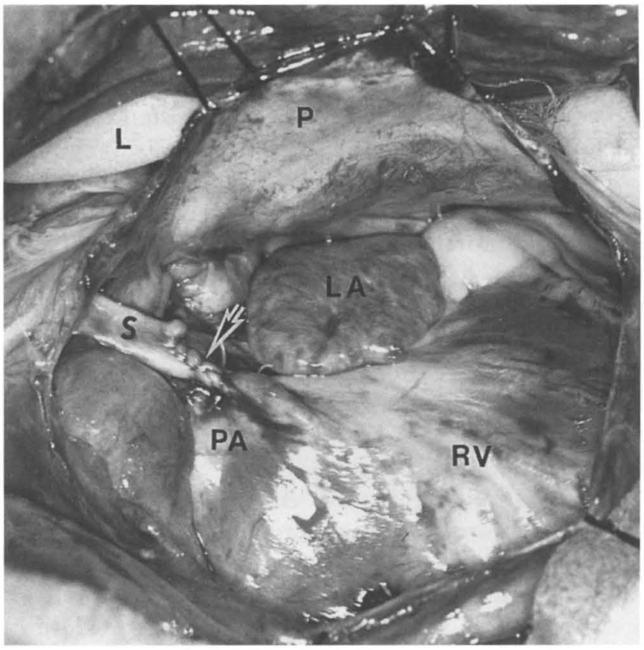


FIGURE 39–6

Left lateral thoracotomy at the 4th intercostal space. The lungs *(L)* are reflected posteriorly. The left subclavian artery *(S)* was rotated and anastomosed to the main pulmonary artery *(PA)* in an end-to-side pattern *(arrow)*. This Blalock anastomosis is used to palliate clinical signs associated with tetralogy of Fallot. *P*, pericardium; *LA*, left auricle; *RV*, right ventricle.

POTT'S ANASTOMOSIS AND CONDUIT SHUNTS

Surgical Techniques

Pott's technique uses a simple side-to-side pulmonary artery to aorta anastomosis. Conduit shunt from aorta to pulmonary artery has been described in veterinary medicine for tetralogy. The techniques require microsurgical skills and are probably limited to large institutions at this time.[34] The surgery requires the use of expensive Pott's clamps, which are used to occlude the aorta partially. Techniques of anastomosis are similar to those of other vascular anastomoses, but the size and length of the fistula developed must be carefully monitored lest extreme pulmonary recirculation and left-sided heart failure develop. Accordingly, Pott's anastomosis has fallen in disfavor in human medicine and is not recommended at this time for small animals.

PATENT DUCTUS ARTERIOSUS

Indications and Contraindications

Patent ductus arteriosus (PDA) is nearly always fatal if left untreated, and intervention should be done at the earliest possible date. Fortunately, left-to-right shunting PDA can be cured surgically with a success rate of over 95 percent.[35–38] Small size is not a contrain-

dication for surgical repair[36]; however, atrial fibrillation (particularly in large, older dogs) confers a significantly lower success rate.[37] Increasingly, nonsurgical transcatheter coil occlusion of the persistently patent ductus arteriosus is being used in place of surgery.[7–9]

Smaller breeds with PDA tend to develop left-sided heart failure at an earlier age and over a shorter time period than do larger breeds. In our experience, half the dogs with PDA presented for surgery have mitral regurgitation associated with left ventricular and mitral annulus dilation resulting from volume overload. These animals are more prone to develop pulmonary edema. However, when they are administered furosemide 12 hours prior to surgery, they are at no increased anesthetic risk.

Preoperative care is most concerned with animals who have severe mitral regurgitation or pulmonary edema. Congestive heart failure should be treated with vigorous diuresis and other agents as needed to effect a compensated state prior to surgery. PDA closure should then be accomplished without delay.

Occasionally, animals with PDA may develop malignant pulmonary hypertension and secondary right-to-left shunt (Eisenmenger's syndrome), particularly dogs who live at high altitudes. More frequently, right-to-left shunting in dogs results from persistence of the fetal circulation, so that the embryologic right-to-left pulmonary to aortic flow persists into the neonatal period. Right-to-left shunting PDA, regardless of cause, is a contraindication to surgery or coil occlusion.

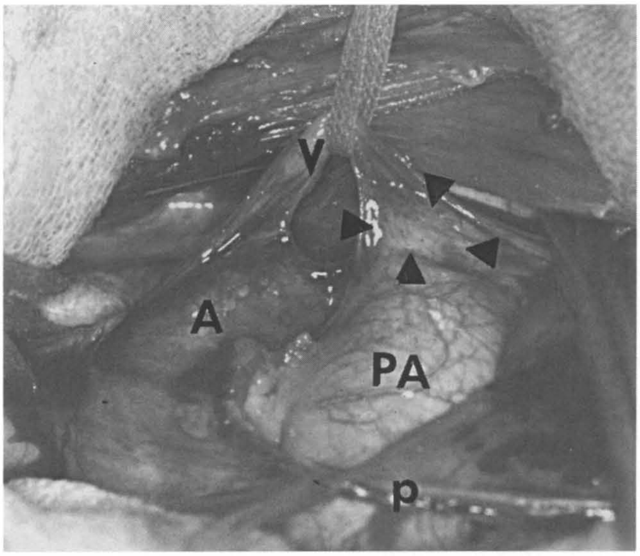


FIGURE 39–7

Left lateral thoracotomy at the 4th intercostal space. The lungs have been reflected, the vagus nerve *(V)* his been elevated *(top)*, and the phrenic nerve *(p)* is visualized at the bottom. The patent ductus arteriosus is exposed and is barely visible (within *arrows*) between the aorta *(A)* (dorsal) and the pulmonary artery *(PA)* (ventral). The patent ductus arteriosus lies medial to the vagus nerve.

STANDARD DISSECTION TECHNIQUE

Surgical Techniques

Left lateral thoracotomy at the 4th intercostal space is performed. Preoperative atropine administration blunts the parasympathetic stimulation that occurs when the vagus nerve is manipulated in the process of visualizing the ductus. The left cranial lung lobe is rotated posteriorly, revealing the right ventricular outflow tract and descending aorta. An incision is made into the pericardium parallel to and between the vagus and phrenic nerves. The vagus nerve is identified, looped with umbilical tape, and elevated along with the pericardium off the heart and the aorta. Using right-angle forceps, the normal cleavage plane between the cranial dorsal aorta and posterior ventral pulmonary artery is opened. This plane lies just cranial to the ductus. The ductus can now be visualized beneath the elevated vagus nerve, ventral to the aorta and dorsal to the pulmonary artery (Fig. 39–7). The right-angle forceps is then passed beneath the aorta, posterior to the ductus, and around and down to the previously opened cleavage plane. With the right-angle forceps beneath the ductus, two double-O silk sutures are carried behind the ductus, positioned, and tied. The aortic side of the ductus is tied first. Closure is routine.

In dogs heavier than 7 kg, safety ties may be placed on the arch vessels in an effort to control bleeding if it occurs. These are simply accomplished with umbilical tape by looping the left subclavian and brachycephalic arteries and placing a Blalock tourniquet around the descending aorta. An additional incision is made in the pericardium ventral to the phrenic nerve. With these safety measures, bleeding produced by a tear in the ductus can be controlled. The umbilical tapes are tightened on the subclavian and brachycephalic arteries and on the aorta to control all systemic arterial backflow to the ductus. A large vascular clamp is placed across the pulmonary artery and aorta through the opening made in the pericardium at the transverse sinus of the pericardium. This stops all forward bleeding from the aorta and the pulmonary artery. Once back-bleeding from the pulmonary artery is stopped, all blood flow in the circulatory system is stopped, and a clamp or suture can be placed on the torn ductus. Duration of occlusion should be less than 2 minutes. Animals smaller than 7 kg would hemorrhage excessively before the safety sutures and clamps could be applied; therefore, this safety technique is generally not recommended in these patients.

Postoperative management of PDA patients is uncomplicated and routine. The owner should be cautioned that the animal should not engage in strenuous exercise during the ensuing 3 weeks, but no other restrictions are required.

JACKSON TECHNIQUE

Surgical Techniques

An additional technique for suture placement around the ductus eliminates dissection beneath the friable ductus. This Jackson technique[38] requires passing one end of the suture beneath the aorta cranial to the ductus and out the prepared cleavage point between the aorta and pulmonary artery. The other end of the suture is carried under the aorta from dorsal to ventral posterior to the ductus (Fig. 39–8) after dissecting the back wall of the aorta free of the mediastinal tissue. When the ends of the suture are pulled together and tied, the suture is pulled beneath the aorta around the ductus, thereby occluding it.

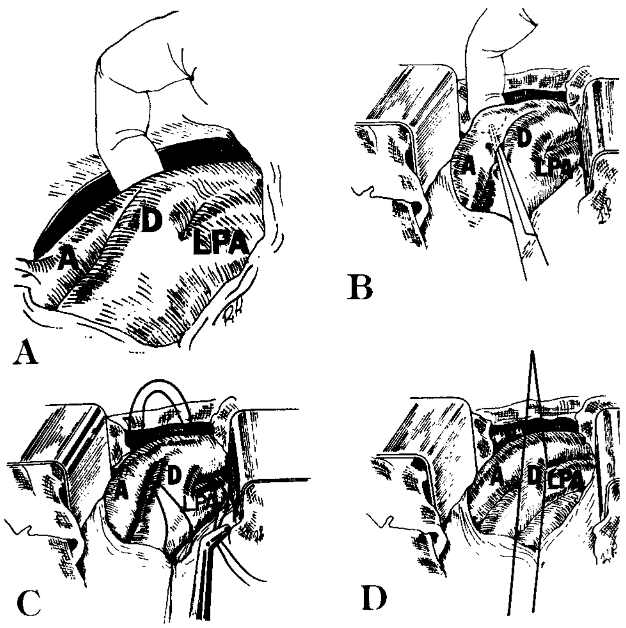


FIGURE 39–8

Suture placement for ligation of the patent ductus arteriosus using the Jackson technique. (A) Prior to suture placement, the mediastinal tissues are bluntly dissected dorsal and cranial to the aorta *(A)*, from the left subclavian artery to the patent ductus arteriosus *(D)*. The aorta is freed from surrounding tissue on its medial side. *LPA,* left pulmonary artery. (B) Suture positioning is illustrated prior to ligating the patent ductus arteriosus. Right-angle forceps are carefully passed between the aorta and the pulmonary artery in the cleavage plane posterior to the arch of the aorta, ventral to the descending aorta, cranial to the ductus arteriosus, and dorsal to the pulmonary artery. If further dissection is necessary, it should be performed near the strong aorta. The midpoint of the 00-silk suture is grasped and the suture is pulled between the aorta and the pulmonary artery cranial to the ductus. (C) Similarly, the forceps is passed under the aorta posterior to the ductus; the ends of the suture are grasped and then pulled laterally caudal to the ductus. Care should be taken to assure that forceps placement is dorsal to the left pulmonary artery. (D) Gentle traction is applied to the suture, causing it to be positioned around the ductus; the cranial looped end is cut, leaving two sutures. The aortic side is tied first; 30 seconds later the pulmonary artery side (not shown) is tied. The knot types should be either a granny (so that the second throw can be slipped down tight) followed by a square knot, or a surgeon's tie (so that the first throw will not loosen).

SURGICAL CONSIDERATIONS FOR RECANALIZATION FOLLOWING DUCTAL LIGATION

Approximately 1.5 percent of ductus ligations will recanalize, typically within 2 months after the initial surgical repair. The cause of recanalization is frequently unknown; however, infection at the surgery site may precipitate it. When recanalization has occurred, the animal should be reoperated and the ductus surgically divided. Dissection is difficult and requires the placement of expensive patent ductus clamps. The ductus is divided between the clamps and sutured with 6-0 vascular suture. This technique is extremely difficult, carries a high risk, and should be considered only by surgeons experienced in vascular surgery.

ATRIOVENTRICULAR VALVE DISEASE, VALVE REPLACEMENT AND REPAIR

MITRAL VALVE DISEASE

Chronic acquired valve disease is the most common cardiac disorder in dogs (chapter 25).[39] Medical therapy constitutes the standard form of management (chapter 12), yet in a significant number of these dogs the disease is inexorably progressive to congestive heart failure and death. Accordingly, surgical replacement or repair of the atrioventricular valves has been reported in a small number of dogs.[40–44] However, the extensive costs and the requirements for cardiopulmonary bypass and valve replacement and advanced surgical training limit these techniques for all but a few patients at several selective institutions. Ideally, potential surgical candidates must be in good health, have normal myocardial function (this precludes dogs with dilated cardiomyopathy), and receive valve replacements well before end-stage disease has developed.

One case of mitral valve reconstruction has been reported in a toy breed dog performed in association with a private practice.[43] The valve was partially removed and reconstructed in a manner to reduce the valve annulus and the associated regurgitation. Since the valve was not replaced, there was no need for expensive valve prosthesis; postoperative long-term anticoagulation was not needed; and the surgery bypass time was reduced. A study in 1997 supported the feasibility of low-flow hypothermic cardiopulmonary bypass in small dogs (< 10 kg).[45]

Another approach to canine mitral valve surgery has taken an entirely different tack and involves reduction of the mitral valve annulus size without cardiopulmonary bypass.[44] This technique uses an external-internal suture placed around the mitral annulus; when tightened, it constricts the mitral annulus and thus reduces

the degree of mitral regurgitation. This suture is placed from outside the heart with the help of a special guide. Although case numbers are currently small and mortality is still high, this technique appears to hold promise.

Mitral valve stenosis may be congenital or acquired. These conditions are rare in small animal veterinary medicine. Surgical considerations are therefore not addressed here.

TRICUSPID VALVE DISEASE

Severe right-sided heart volume overload resulting from tricuspid insufficiency may result in effusions (pleural, pericardial, or abdominal) or, less commonly, peripheral edema. Surgical repair of the tricuspid valve is currently not performed in veterinary medicine. Consequently, tricuspid insufficiency and associated clinical abnormalities are treated medically. Although surgery for tricuspid dysplasia, or Ebstein's anomaly, has been performed,[46] outcome is generally unsatisfactory, and surgery cannot be recommended at this time. In addition, tricuspid valve replacement requires long-term anticoagulation, which has not proved to be reliable in the dog. Tricuspid stenosis, a very rare condition, has been relieved by balloon valve dilation.[5]

VASCULAR RING ANOMALIES

Indications and Contraindications

For the purposes of this discussion, vascular ring anomalies are divided into two groups: persistent right aortic arch and others. Because of the high incidence of persistent right aortic arch (95 percent),[47] this lesion is generally assumed to be present and is easily verified by a contrast study following a barium swallow. The differential diagnosis of persistent right aortic arch or other vascular ring anomalies usually requires angiography. However, since the surgical exposure is similar for other types of vascular ring anomalies, further diagnostic workup is usually not recommended. Treatment involves surgical division of the tissues obstructing the esophagus.

Surgical Techniques

Surgery for persistent right aortic arch, as in other vascular ring anomalies, is performed through a lateral thoracotomy in the left 4th intercostal space. The dilated esophagus is readily identified, and the obstructive vascular structure can be found immediately caudal to the dilation of the esophagus (see Fig. 24–61). In persistent right aortic arch, the rightward aorta is usually not visualized since it is to the right of the dilated esophagus. The tight, white, glistening band of the ligamentum arteriosum or PDA may be identified as it obstructs the esophagus. With blunt dissection, the obstructing band is isolated, double ligated, and divided. Approximately 10 percent of the bands are patent. At the dorsal, rightward end of the band, the aorta may be just visualized. The ventral, leftward pulmonary artery is easily visualized. After the ligamentum arteriosum is divided, the esophagus is bluntly freed from surrounding mediastinal tissue, which might act as a continuing constriction by adhesion. At this time, the esophageal stethoscope should be passed from the distended esophagus through the constricted area into the caudal esophagus.

If additional anomalous vessels are identified at the time of surgery, they can be divided. In cases of double aortic arch, a decision must be made as to which arch to sacrifice. Preferably, the one without branches or the least prominent arch should be chosen. If the left aortic arch appears to be the largest, the patient's chest should be closed. At a later convenient time, a right thoracotomy should be performed and the right aortic arch divided. Postoperative management of other vascular ring anomalies is similar to that of persistent right aortic arch. The prognosis for treatment of aberrant arch vessels is very good. Prognosis for success with double aortic arch is very poor, but these lesions occur only rarely.

If the esophagus is still somewhat constricted, bougienage should be performed. This can be accomplished using a Foley catheter with the balloon placed at the constricted area. After freeing the esophagus and dilating it internally, the chest is closed in routine manner.

Postoperatively, the patient should be fed small amounts of liquid diet frequently, preferably in an elevated position, until normal esophageal activity returns. The animals can be slowly returned to a normal feeding plan in a period of 2 to 6 weeks. In severely affected animals, esophageal motility may never return.

The prognosis depends on the severity of esophageal distention and associated esophageal injury. If surgery is performed before severe esophageal distention and pocketing occur, the results can be excellent, although a recent study suggested that persistence of megaesophagus and regurgitation in the early postoperative period did not indicate a poor long-term outcome.[48]

COR TRIATRIATUM AND CAVAL ANOMALIES

These rare conditions are generally correctable with surgery. Cor triatriatum is poorly responsive to medical therapy. Atrial septectomy during inflow occlusion, when successful, resolves clinical signs.[49] Successful sur-

gical dilation and tearing of the anomalous membrane has been reported.[49a] A right 5th intercostal thoracotomy approach is used. Both cava and azygos veins are encircled with umbilical tapes that are incorporated in Rumel snares. The pericardium is opened ventral to the phrenic nerve. The portion of right atrial wall over the septum separating the cranial and caudal right atrial chambers is entrapped with a tangential vascular clamp. The atrium within the clamp is incised. Venous inflow of the vena cava and azygos veins is occluded and the heart is permitted to empty (circulatory arrest should be less than 4 minutes). The atrial wall clamp is removed and the abnormal septum is excised. The atrium is closed with a simple continuous suture pattern and oversewn.

Caudal vena caval abnormalities are rare. Reported cases include extraluminal compressive masses and intraluminal obstruction from neoplasia, trauma, and membranes. Surgical correction provides successful management in many instances.[50–52]

SURGICAL REMOVAL OF ADULT HEARTWORMS

Indications and Contraindications

Although rarely needed and uncommonly performed, surgical removal of heartworms has been a successful and valuable treatment for selected patients with severe heartworm disease—particularly, because it is the only successful treatment for severe caval syndrome.[53, 54] These dogs can be managed by right jugular venotomy and removal of the heartworms by alligator forceps.

Surgical Technique

CAVAL SYNDROME. Local anesthetic infiltration over the right jugular vein is usually all that is necessary, since these patients are prostrate and require little, if any, sedation. Fluoroscopy can permit visualization during manipulation but is not necessary.

An incision is made over the right jugular furrow. The jugular vein is identified, occluded distally, and opened. Long alligator forceps are introduced into the jugular vein and advanced into the heart, and worms are grasped and removed. At completion, the jugular vein is ligated and the skin closed. The technique is effective in approximately 85 percent of dogs with caval heartworm syndrome, which would otherwise be fatal. The technique has also been used to reduce the worm load prior to medical treatment.

OTHER APPLICATIONS. In rare situations, dogs with severe heartworm infection may be considered as candidates for surgical adult worm removal. One situation includes dogs that had concurrent severe renal or hepatic dysfunction, restricting the use of arsenical compounds. However, with melarsomine hydrochloride, the therapeutic index is greater than with thiacetarsamide. Another situation involves the valuable field dog that would be compromised by pulmonary embolization due to routine adulticide treatment. The surgical techniques that are effective for this type of heartworm disease were previously described for PS and involve right ventriculotomy, using alligator forceps rather than the bistoury, and worm removal by the forceps. Pulmonary arteriotomy after inflow occlusion and direct removal of the worms is a preferable procedure. The surgical techniques are relatively simple and have a lower morbidity in critical heartworm patients than does routine medical therapy. Open heart surgery may allow removal of adult heartworms.[55]

PERICARDIECTOMY

Indications and Contraindications

Pericardiectomy is a technically simple procedure used for management of some cases of chronic pericardial disease in the dog.[56] Occasionally, cases of severe, chronic pericardial disease cause marked pericardial thickening with extensive vascularization and granulomatous changes (chapter 29), making surgery very difficult. Pericardial windows may not be effective in these cases because pericardial adhesions form postoperatively. Even when surgical management seems effective, pericardial effusion can recur as much as 4 years later in some cases.[57]

Surgical Techniques

Median sternotomy provides the best surgical exposure since removal of most or all pericardium is required for successful pericardiectomy. Electrocautery is advised for this dissection because of the vascular nature of the affected pericardium. Unfortunately, if the procedure is not curative, persistent postoperative bleeding or effusion may be life threatening, since bleeding will interfere with healing of the median sternotomy incision. However, because untreated chronic pericardial disease is eventually fatal, the risk-benefit ratio favors surgical intervention.

Median sternotomy is performed as described previously, incising approximately the posterior two thirds to three fourths of the sternum. The phrenic nerves are carefully dissected free of the pericardium, and the pericardium is removed using electrosurgery as close to the heart base as can safely be accomplished. Strict control of hemorrhage must be maintained. Chest closure is routine. Postoperative chest drainage should be

maintained for at least 24 hours, or until little additional pleural effusion is collected.

If adequate removal of the pericardium is accomplished and postoperative effusion is limited, pericardiectomy is a very effective procedure for chronic pericardial effusion and tamponade. Excessive postoperative effusion or inadequate removal of pericardium may produce unacceptable results, including heart failure and death.

CARDIAC TUMORS

Right atrial hemangiosarcoma and chemodectoma (the most common cardiac neoplasia) generally are not amenable to surgery; occasionally, however, surgical intervention with palliative pericardiectomy has produced somewhat favorable results.[57, 58]

HEMANGIOSARCOMA. This metastatic tumor is often associated with the right heart, particularly the right atrium. It is usually detected in dogs who are presented for signs associated with pericardial tamponade. If identified early without gross evidence of multiorgan metastasis, it can sometimes be surgically removed, particularly when it is localized to the right auricular appendage. Surgery involves isolating the tumor with a vascular clamp beneath the base of the tumor, excision, and closure of the atrium. Alternatively, the right auricle can be excised with a thoracoabdominal stapling instrument when the tumor is located in this appendage.[59] Unfortunately, the aggressive nature of the tumor, the typical advanced stage at the time of detection, and perioperative difficulties have contributed to poor results.

CHEMODECTOMA ("HEART-BASE TUMOR"). The term "heart base tumor" has been loosely applied to any tumor situated at the cardiac base. Chemodectoma is the most common neoplasia located in that area, although other malignancies and non-neoplastic masses can also occur. Chemodectoma is a relatively slow-growing, locally invasive cancer. It is commonly located between the aorta and pulmonary artery and can sometimes grow to enormous size before clinical signs (pericardial or pleural effusion) are recognized. Surgical excision of the tumor from the wall of the great vessels and atria, followed by chemotherapy or radiation therapy, has been advocated. Electrocautery is used to decrease hemorrhage. Although some cases appear to respond, clinical outcome is usually unrewarding. Palliative pericardiectomy may be effective when clinical signs are associated with chronic pericardial effusion.

PACEMAKER THERAPY

Symptomatic bradycardia in dogs and cats unresponsive to medical therapy may be treated by cardiac pacing. For many years, implantation of a permanent pacemaker required a thoracotomy or abdominal transdiaphragmatic approach through which an epicardial electrode was attached to the left ventricular apex. Transvenous lead insertion of a right ventricular endocardial electrode has become popular due to the relatively simpler nature of this technique. Chapter 20 discusses pacemaker therapy in detail.

REFERENCES

1. Fossum TW. Small Animal Surgery. St Louis, Mosby–Year Book, 1997
2. Orton EC (ed): Advances in cardiovascular surgery. Semin Vet Med Surg 9:1, 1994
3. Brown WA, Thomas W. Balloon valvuloplasty of tricuspid stenosis in a Labrador retriever. J Vet Intern Med 9:419, 1995
4. Buchanan JW. Surgery versus catheter valvuloplasty for the treatment of common cardiac defects in small animals. Proceedings WSAVA World Congress, 1993, p 343
5. deLellis LA, Thomas WP, Pion PD. Balloon dilation of congenital subaortic stenosis in the dog. J Vet Intern Med 7:1532, 1993
6. Fox PR, Bond BR, Sommer RJ. Nonsurgical transcatheter coil occlusion of patent ductus arteriosus in two dogs using a preformed nitinol snare delivery technique. J Vet Intern Med (in press)
7. Snaps FR, McEntee K, Saunders J, Dondelinger RF. Treatment of patent ductus arteriosus by placement of intravascular coils in a pup. J Am Vet Med Assoc 207:724, 1995
8. Schneider M, Hagel K-J, Schneider I, Neu H. Transvenös Coil-Embolisation zum Verschluss des persistierenden Ductus arteriosus (Botalli) bei einem Hund. Kleintierpraxis 41:685 1996
9. Fox PR, Sos TA, Bond BR. Nonsurgical removal of a catheter embolus from the heart of a dog. J Am Vet Med Assoc 187:275, 1985
10. Graves TK, Lehmkuhl LB, Peterson J, et al. Transvenous removal of intravenous catheter emboli from the right-side heart of a cat and from the left caudal pulmonary artery of a dog. J Am Anim Hosp Assoc 20:327, 1993
11. Ripps JH, Henderson AR. Congenital pulmonic valvular stenosis in a dog: report of a case successfully treated surgically. J Am Vet Med Assoc 123:292, 1953
12. Brock RC. Pulmonary valvotomy for the relief of congenital pulmonary stenosis. Br Med J 1:1121, 1948
13. Swan H, Zeavin J, Blount SG Jr, Virtue RW. Surgery by direct vision in the open heart during hypothermia. J Am Med Assoc 153:1081, 1953
14. Buchanan JW. Pulmonic stenosis caused by a single coronary artery in dogs: four cases (1965–1984). J Am Vet Med Assoc 196:115, 1990
15. Breznock EM, Wood GL. A patch-graft technique for correction of pulmonic stenosis in dogs. J Am Vet Med Assoc 169:1090, 1970
16. Orton CE, Bruecker KA, McCracken TO. An open patch-graft technique for correction of pulmonic stenosis in the dog. Vet Surg 19:148, 1990

17. Ford RF, Spaulding GL, Eyster GE. Use of an extracardiac conduit in the repair of supravalvular pulmonic stenosis in a dog. J Am Vet Med Assoc 172:922, 1978
18. Kienle RD, Thomas WP, Pion PD. The natural clinical history of canine congenital subaortic stenosis. J Vet Intern Med 8:423, 1994
19. Breznock EM, Whiting P, Pendrays D, et al. Valved apicoaortic conduit for relief of left ventricular hypertension caused by discrete subaortic stenosis in dogs. J Am Vet Med Assoc 182:51, 1983
20. Komtebedde J, Ilkiw J, Follette DM, et al. Resection of subvalvular aortic stenosis: surgical and perioperative management in seven dogs. Vet Surg 22:419, 1993
21. Monnet E, Orton C, Gaynor JS, et al. Open resection for subvalvular aortic stenosis in dogs. J Am Vet Med Assoc 209:1255, 1996
22. Harrison KJ, Davidson CJ, Leithe ME, et al. Serial left ventricular performance evaluated by cardiac catheterization before, immediately after and at 6 months after balloon aortic valvuloplasty. J Am Coll Cardiol 16:1351, 1990
23. Linn KA, Orton EC. Closed transventricular dilation of discrete subvalvular aortic stenosis in dogs. Abstract. Proc Am Coll Vet Surg, 1991
24. Tashjian RJ, Das KM, Palich WE, et al. Studies on cardiovascular disease in the cat. Ann NY Acad Sci 127:581, 1965
25. Monnet E, Orton EC, Gaynor J, et al. Diagnosis and surgical repair of atrioventricular septal defects in two dogs. J Am Vet Med Assoc 211:569, 1997
26. Eyster GE. Atrial septal defect and ventricular septal defect. Semin Vet Med Surg 9:227, 1994
26a. Monnet E, Orton C, Gaynor J, et al. Diagnosis and surgical repair of partial atrioventricular septal defects in two dogs. J Am Vet Med Assoc 211:569, 1997
27. Eyster GE, Anderson LK, Krehbiel JD, et al. Surgical repair of atrial septal defect in a dog. J Am Vet Med Assoc 169:1081, 1976
28. Patterson DF. Canine congenital heart disease: epidemiology and etiological hypothesis. J Small Anim Pract 12:263, 1971
29. Braden TD, Appleford MD, Hartsfield SM. Correction of a ventricular septal defect in a dog. J Am Vet Med Assoc 161:507, 1972
30. Weirich WE, Blevins WE. Ventricular septal defect repair. Vet Surg 7:2, 1978
31. Mann PG, Stock JE, Sheridan JP. Pulmonary artery banding in a cat: a case report. J Small Anim Pract 12:45, 1971
32. Eyster GE, Whipple RD, Anderson LK, et al. Pulmonary artery banding for ventricular septal defect in dogs and cats. J Am Vet Med Assoc 170:434, 1977
32a. Lew LJ, Fowler JD, McKay R, et al. Open-heart correction of tetralogy of Fallot in an acyanotic dog. J Am Vet Med Assoc 213:652, 1998
33. Eyster GE, Braden TD, Appleford MD, et al. Surgical management of tetralogy of Fallot. J Small Anim Pract 18:387, 1977
34. Miller CW, Holmberg DL, Bowen V, et al. Microsurgical management of tetralogy of Fallot in a cat. J Am Vet Med Assoc 186:708, 1985
35. Buchanan JW. Patent ductus arteriosus. Semin Vet Med Surg (Small Anim) 9:168, 1994
36. Birchard SJ, Bonagura JD, Fingland RB. Results of ligation of patent ductus arteriosus in dogs: 201 cases (1969–1988) J Am Vet Med Assoc 196:2011, 1990
37. Eyster GE, Eyster JT, Cords GB, et al. Patent ductus arteriosus in the dog: characteristics of occurrence and results of surgery in one hundred consecutive cases. J Am Vet Med Assoc 168:435, 1976
38. Jackson WF, Henderson RA. Ligature placement in closure of patent ductus arteriosus. J Am Anim Hosp Assoc 15:55, 1979
39. Detweiler DK, Hubben K, Patterson DF. Survey of cardiovascular disease in dogs. Preliminary report on the first 1000 dogs surveyed. Am J Vet Res 21:329, 1960
40. Eyster GE, Weber W, Chi S, et al. Mitral valve prosthesis for correction of mitral regurgitation in a dog. J Am Vet Med Assoc 168:1115, 1976
41. Breznock EM, Bauer T, Strack D, et al. Prosthetic mitral and tricuspid valve implantation in dogs using deep surface hypothermia. Proc Am Coll Vet Surg, 1983
42. Klement P, Feindel CM, Scully H, et al. Mitral valve replacement in dogs: surgical technique and postoperative management. Vet Surg 16:231, 1987
43. Boggs LS, Dewan SJ, Ballard SE. Mitral valve reconstruction in a toy-breed dog. J Am Vet Med Assoc 209:1872, 1996
44. Kertsetter K, Buchanan JW. Mitral valve repair. Proc Am Coll Vet Surg, 1986
45. Lew LJ, Fowler DJ, Egger CM, et al. Deep hypothermic low-flow cardiopulmonary bypass in small dogs. Vet Surg 26:281, 1997
46. Eyster GE, Anderson LK, Evans AT, et al. Ebstein's anomaly: a report of three cases in the dog. J Am Vet Med Assoc 170:709, 1977
47. van den Ingh TSAM, van der Linde-Sipman JS. Vascular rings in dogs. J Am Vet Med Assoc 164:939, 1974
48. Muldoon MM, Birchard SJ, Ellison GW. Long-term results of surgical correction of persistent right aortic arch in dogs: 25 cases (1980–1995). J Am Vet Med Assoc 210:1761, 1997
49. Fossum TW, Miller MW. Cor triatriatum and caval abnormalities. Semin Vet Med Surg (Small Anim) 9:177, 1994
49a. Wander KW, Monnet E, Orton EC. Surgical correction of cor triatriatum sinister in a kitten. J Am Anim Hosp Assoc 34:383, 1998
50. Malik RM, Hunt GB, Chard RB, et al. Congenital obstruction of the caudal vena cava in a dog. J Am Vet Med Assoc 197:880, 1990
51. Cornelius L, Mahaffey M. Kinking of the intrathoracic caudal vena cava in five dogs. J Small Anim Pract 26:67, 1985
52. Crowe DT Jr, Lorenz MD, Hardie EM, et al. Chronic peritoneal effusion due to partial caudal vena caval obstruction following blunt trauma: diagnosis and successful surgical treatment. J Am Anim Hosp Assoc 20:231, 1984
53. Jackson WF, Seymour WG, Growney PG, Otto GF. Surgical treatment of the caval syndrome of canine heartworm disease. J Am Vet Med Assoc 171:1065, 1977
54. Rawlings CA, Calvert CA, Glaus TM, Jacobs GJ. Surgical removal of heartworms. Semin Vet Med Surg (Small Anim) 9:200, 1994
55. Shiang H, Jurado R, Liu SK, et al. Nine-month evaluation of dogs after open-heart surgical removal of heartworms. J Am Vet Med Assoc 190:1425, 1987
56. Berg R, Wingfield WE, Hoopes PJ. Idiopathic hemorrhagic pericardial effusion in 8 dogs. J Am Vet Med Assoc 185:998, 1984
57. Berg J. Pericardial disease and cardiac neoplasm. Semin Vet Med Surg (Small Anim) 9:185, 1994
58. Aronsohn M. Cardiac hemangiosarcoma in the dog: a review of 38 cases. J Am Vet Med Assoc 187:922, 1985
59. Wykes PM, Rouse GP, Orton EC. Removal of five canine cardiac tumors using a stapling instrument. Vet Surg 15:103, 1986

Appendix A

Recommendations for Diagnosis of Heart Disease and Treatment of Heart Failure in Small Animals

This document was created by the ***International Small Animal Cardiac Health Council*** (below), starting in May of 1992, to provide guidelines for diagnosing common cardiac diseases in small animals and for treating the heart failure that occurs secondary to these diseases.

The International Small Animal Cardiac Health Council has included the following members:

Dr. John Bonagura, University of Missouri; Dr. Claudio Bussadori, Milan, Italy; Dr. David Church, The University of Sydney, Australia; Dr. Peter G. G. Darke, University of Edinburgh, Scotland; Dr. Philip Fox, Animal Medical Center, NY; Dr. Robert Hamlin, The Ohio State University; Dr. Bruce Keene, North Carolina State University; Dr. Mark D. Kittleson, University of California; Dr. Chris Lombard, Universität Bern, Switzerland; Dr. Takeo Minami, Japan; Dr. Sydney Moïse, Cornell University; Dr. Michael O'Grady, University of Guelph, Canada; Dr. Paul D. Pion, University of California; Dr. Jean Louis Pouchelon, Alfort National Veterinary School, France; Dr. David Sisson, University of Illinois; Dr. William P. Thomas, University of California; Dr. Larry P. Tilley, Santa Fe, NM; and Dr. Yoshihisa Yamane, Japan

The ***International Small Animal Cardiac Health Council*** activities are supported by an educational grant from Merial Ltd.

PATHOPHYSIOLOGY OF HEART DISEASE LEADING TO HEART FAILURE

HEART DISEASE is defined as the presence of any cardiac finding outside the accepted limits of normality, such as a systolic murmur or systolic click heard on auscultation, a bundle branch block on the electrocardiogram, or reduced wall motion on the echocardiogram.

The major functions of the cardiovascular system are to maintain normal (1) systemic arterial blood pressure, (2) blood flow (cardiac output), and (3) venous and capillary pressures. When cardiac disease becomes severe, the ability of the cardiovascular system to maintain these functions deteriorates. Consequently, heart failure may manifest as edema resulting from high capillary pressure, low cardiac output (hypoperfusion), or low blood pressure (hypotension).

MYOCARDIAL FAILURE is defined as a decrease in myocardial contractility. Many types of heart disease (e.g., dilated cardiomyopathy) result in myocardial failure. Although patients with myocardial failure commonly develop signs of

heart failure, myocardial failure may be present when heart failure is not. Myocardial failure is not a consistent feature of heart failure and in many cardiac diseases myocardial systolic function is normal, yet heart failure is present (e.g., hypertrophic cardiomyopathy, mitral regurgitation in small dogs, and chronic pericardial tamponade).

ACUTE HEART FAILURE can be severe enough to lead to cardiogenic shock. Hypoperfusion and hypotension usually prevail because chronic compensatory mechanisms have not had time to become effective.

CHRONIC HEART FAILURE usually allows time to physiologically compensate for heart disease. Compensation commonly takes the form of renal sodium and water retention, which produces an increase in circulating blood volume. As venous return increases, the myocardium in the affected ventricle is stretched, stimulating it to grow into a larger chamber (*volume overload* or *eccentric hypertrophy*). The increase in end-diastolic volume provided by volume overload hypertrophy allows the affected ventricle to accommodate a larger diastolic volume without increasing diastolic ventricular pressure and to pump more blood for any given amount of myocardial shortening (shortening fraction).

Renal sodium and water retention is stimulated through a number of different mechanisms that are activated by a decrease in systemic and, therefore, renal blood flow or circulating blood volume. The renin-angiotensin-aldosterone system (RAAS) is one of the most important mechanisms for stimulation of salt and water retention. When the ability of the ventricle to enlarge reaches a maximum and becomes overwhelmed, the kidneys continue to retain salt and water because of the continued suboptimal cardiac output and renal perfusion. At this stage, the salt and water retention increases diastolic ventricular pressure to a clinically significant level.

SIGNS OF HEART FAILURE are associated with (1) diseases of the left side of the heart, manifested by pulmonary congestion and edema, called *left-sided congestive heart failure.* Congestion and edema formation are the most common manifestations of chronic heart failure, so the term "congestive heart failure" is often used synonymously with heart failure; (2) diseases of the right side of the heart, which manifest differently among species. In dogs and cats, *right-sided congestive heart failure* usually results in ascites and, occasionally, pleural or pericardial effusion or subcutaneous edema. Also, congestive right and left heart failure together commonly produce pleural effusion. Chronic heart failure patients can also have clinical signs referable to poor perfusion *(low-output failure),* but these signs are less common and generally occur late in the course of the disease. These animals do not usually become clinically hypotensive.

DEFINITION OF HEART FAILURE

HEART FAILURE occurs when heart disease becomes severe enough to overwhelm the compensatory mechanisms of the cardiovascular system. Heart failure is not a disease. Heart failure is present when a mechanical inadequacy of the heart results in elevated venous and capillary pressures, leading to congestion and edema formation in the tissues (CONGESTIVE or BACKWARD HEART FAILURE) or inadequate cardiac output (FORWARD or LOW-OUTPUT HEART FAILURE) or both. The presence of identifiable heart disease does not in any way imply that heart failure is present or will ever manifest as a clinical problem.

While there are many proposed *definitions of heart failure,* none is universally accepted. Four currently employed definitions include:

An inability of the heart to deliver enough blood to the peripheral tissues to meet metabolic tissue demands. A decreased cardiac output and a rise in atrial pressures are the hallmarks of the syndrome. In mild forms of heart failure, cardiac output falls and atrial pressures rise in response to physical exertion. As the heart failure syndrome worsens, clinical signs are detectable at lower levels of exertion and finally are apparent at rest. (Parmley WW, Chatterjee K. Principles in the management of congestive heart failure. *In* Parmley WW, Chatterjee K: Cardiology. Philadelphia, JB Lippincott, 1988, p 1.)

Pathophysiologic state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues or do so only at an elevated filling pressure. (Braunwald E: Pathophysiology of heart failure. *In* Braunwald E. Diseases of the Heart, 4th ed. Philadelphia, WB Saunders, 1992, p 393).

When the cardiovascular system fails to circulate sufficient blood to meet the metabolic demands of the body for nutrients or when the blood backs up within a venous or capillary bed, the patient manifests a complex of clinical signs. These clinical signs resulting from cardiac dysfunction translate into a reduced quality of life and/or longevity.

"Heart failure is a pathophysiologic condition that becomes clinically apparent when heart disease causes systolic or diastolic cardiac dysfunction or both, severe enough to produce clinical signs referable to edema or peripheral hypoperfusion, or a combination thereof, at rest or with exercise."

CLASSIFICATION OF HEART FAILURE SEVERITY

It is useful to think of heart disease and failure as a continuum that may progress from heart disease to the preclinical phase to a phase with overt clinical signs.

1. *Heart disease* includes numerous anatomic and physi-

ologic abnormalities of diverse etiology that may or may not become clinically significant to the patient.
2. The *preclinical phase* has identifiable cardiac structural abnormalities (e.g., by radiography, electrocardiography, echocardiography). However, these are not apparent to the owner because of compensatory mechanisms that inhibit development of clinical signs of heart failure.
3. A *phase with overt clinical signs* evident to the client and clinician heralds advanced congestive heart failure.

HUMAN SCHEME (NEW YORK HEART ASSOCIATION CLASSIFICATION)

Humans with heart disease and heart failure are categorized according to a functional classification scheme based on the signs and symptoms evident at rest and during exercise (New York Heart Association functional classes 1 through 4). This scheme often does not conveniently or appropriately apply to veterinary patients with heart failure primarily because many of these patients do not exercise vigorously. The International Small Animal Cardiac Health Council unanimously concluded that this scheme did not serve the veterinary profession well and that the therapy of heart failure would be better guided by a classification system based on anatomic diagnosis and the severity of clinical signs at rest. Consequently, a new classification scheme was developed that the Council believes is more applicable to the veterinary situation.

INTERNATIONAL SMALL ANIMAL CARDIAC HEALTH COUNCIL HEART FAILURE CLASSIFICATION

THE ASYMPTOMATIC PATIENT

Heart disease is detectable; however, the patient is not overtly affected and does not demonstrate clinical signs of heart failure. Diagnostic findings could include a cardiac murmur, arrhythmia, or cardiac chamber enlargement that is detected by radiography or echocardiography.

This stage is subdivided as follows:

1. No signs of compensation, such as volume or pressure overload ventricular hypertrophy, are evident.
2. Radiographic or echocardiographic evidence of compensation, such as volume or pressure overload ventricular hypertrophy, is present.

The need for treatment here is arguable but not justifiable with currently available data.

MILD TO MODERATE HEART FAILURE

Clinical signs of heart failure are evident at rest or with mild exercise and adversely affect the quality of life. Typical signs of heart failure include exercise intolerance, cough, tachypnea, mild respiratory distress (dyspnea), and mild to moderate ascites. Hypoperfusion at rest is generally not present.

Home treatment is often indicated at this stage.

ADVANCED HEART FAILURE

Clinical signs of advanced congestive heart failure are immediately obvious. These include respiratory distress (dyspnea), marked ascites, profound exercise intolerance, and hypoperfusion at rest. In the most severe cases, the patient is moribund and suffers from cardiogenic shock. Death or severe debilitation is likely without therapy.

This stage is subdivided as follows: (1) home care is possible, (2) hospitalization is mandatory.

SYSTEMATIC APPROACH TO THE DOG OR CAT WITH CARDIAC DISEASE

Signalment

Age, breed, and sex of the patient help formulate a rule-out list and help determine prognosis.

History

Note current and pre-existing diseases. Record current drugs or medications and clinical response to these medicaments. Record presenting clinical signs and duration and progression of the illness.

Physical Examination

In addition to a complete physical examination, perform a thorough cardiovascular examination, including all of the following:

- Auscultation, noting heart rate and presence or absence of the following:
  1. Heart murmur (point of maximum intensity, radiation, loudness, timing, character)
  2. Gallop sound (rhythm)
  3. Other abnormal heart sounds (e.g., splitting of S_1 or S_2, clicks, rubs)
  4. Arrhythmias
  5. Abnormal lung sounds

- Femoral pulse palpation (character, rate, rhythm, pulse deficits)
- Capillary refill time and mucous membrane color evaluation
- Jugular vein observation for distention or pulsation
- Precordial palpation for apical impulse, presence of thrills
- Thoracic percussion
- Abdominal palpation to assess organomegaly and detect ascites

Select from the following diagnostic tests, as indicated on a case-by-case basis:

Electrocardiography

Assess the rate, rhythm, and axis; evaluate the P-QRS-T complex morphology.

Thoracic Radiography

Evaluate cardiac size and shape for evidence of heart disease, cardiomegaly, specific chamber enlargement, and pulmonary and systemic vascular changes. Evaluate for signs of heart failure, such as pulmonary edema and pleural effusion.

Echocardiography

Assess cardiac structure and function to determine the type and severity of the cardiac disease present. Look for fluid accumulation. With radiography, look for possible noncardiogenic causes of current clinical signs.

Clinical Pathology

- Complete blood count (CBC)
- Serum biochemical profile
- Serum electrolyte concentrations (potassium, sodium, chloride, calcium)
- Urinalysis
- Acid-base status (blood pH, P_{CO_2}, bicarbonate)
- Blood gases (arterial and venous oxygen tensions)
- Serum thyroxine concentration
- Cytologic evaluation of effusions
- Heartworm antigen serology, microfilaria detection
- Other tests when appropriate (blood culture, feline leukemia virus tests, feline immunodeficiency [FIV] serology, plasma and whole blood taurine concentration, plasma carnitine concentration, plasma lactate concentration)

CLINICAL FINDINGS IN HEART DISEASE AND HEART FAILURE

1. Client Complaints

- Dyspnea, orthopnea (pulmonary edema, pleural effusion)
- Cough (pulmonary edema, compression of a bronchus by the left atrium)
- Tachypnea (pulmonary edema, pleural effusion)
- Exercise intolerance (low cardiac output, pulmonary edema)
- Abdominal distention (ascites)
- Weakness (low cardiac output)
- Syncope (episodic cessation of cerebral blood flow)
- Weight loss
- Anorexia
- Depression

2. Physical Examination (General)

- Respiratory signs, such as tachypnea, dyspnea
- Ascites
- Distended and possibly pulsating jugular veins
- Abnormal femoral pulses (hypokinetic, hyperkinetic)
- Precordial thrills
- Palpable rhythm irregularities
- Hepatosplenomegaly
- Pale mucous membranes
- Prolonged capillary refill time (> 2 sec)

3. Auscultation

- Murmurs
- Rate and rhythm irregularities
- Abnormal intensity of heart sounds
- Gallop sounds
- Crackles and wheezes (most commonly due to chronic bronchial disease)
- Muffled heart or lung sounds

4. Radiography

- Cardiomegaly (generalized or specific chambers)
- Aortic root or main pulmonary artery bulges
- Pulmonary edema
- Pleural effusion
- Bronchial compression from atrial enlargement
- Pulmonary vascular patterns; for example, pulmonary venous congestion, pulmonary arterial enlargement, pulmonary arterial blunting
- Lung lobe collapse or torsion
- Pulmonary infiltrates, such as inflammatory infiltrates, metastatic lesions

5. Electrocardiography

- Increased or decreased heart rate
- Abnormal cardiac rhythm
- Abnormal mean electrical axis
- Morphologic abnormalities of P wave or QRS complex
- ST segment or T-wave changes

6. Echocardiography

- Anatomic cardiac lesion, such as atrial or ventricular septal defect, atrial enlargement, intra- or extracardiac tumors or thrombi, valvular lesions
- Cardiac hypertrophy patterns: *Eccentric hypertrophy*—volume overload ventricular hypertrophy (commonly termed dilation). *Concentric hypertrophy*—pressure overload ventricular hypertrophy (thickened ventricular myocardium)
- Abnormal ventricular movement: hypo- or hyperkinetic wall motion
- Pericardial or pleural fluid accumulation

7. Clinical Pathology

- Low venous oxygen tension
- Low arterial oxygen tension
- Increased blood lactate concentration
- Prerenal azotemia resulting from severe hypoperfusion or inadequate water intake secondary to malaise
- Mild elevation of liver enzymes
- Hypoproteinemia (congestive right heart failure)
- Elevated serum thyroxine concentration (cats)
- Low plasma or whole blood taurine concentration (cats, some canine breeds)
- Low plasma carnitine concentration (some dogs)
- Electrolyte abnormalities
- Positive heartworm test
- Positive blood culture seen with endocarditis

DEFINITIVE DIAGNOSTIC CRITERIA FOR HEART FAILURE

1. An elevated pulmonary capillary wedge pressure (PCWP), measured with a Swan-Ganz or other end-hole cardiac catheter in a patient with left heart disease, is diagnostic for congestive left heart failure. An increased central venous or right atrial pressure in a patient with right heart disease is diagnostic for congestive right heart failure.
2. Pulmonary edema in a patient with moderate to severe left atrial enlargement is diagnostic for congestive left heart failure.
3. Pulmonary edema in a patient with confirmed acute mitral regurgitation or aortic regurgitation is diagnostic for acute congestive left heart failure.
4. Ascites, and rarely peripheral edema, in a patient with enlarged hepatic veins on ultrasound or obviously distended jugular veins is diagnostic for congestive right heart failure.
5. Ascites, and rarely clinically significant peripheral edema, in a patient with moderate to severe right atrial enlargement is diagnostic for congestive right heart failure.
6. Ascites, and less commonly peripheral edema, in a patient with pericardial disease is diagnostic for congestive right heart failure.
7. Pleural effusion in a patient with right or left heart disease is diagnostic for congestive right or left heart failure. Cardiogenic pleural effusion in cats may be pseudochylous or truly chylous and respond to therapy for congestive heart failure.
8. Low cardiac output or cardiac index in a patient with heart disease is diagnostic for low-output heart failure.
9. Increased blood lactate or low venous oxygen tension at rest or with mild exercise in a patient with congestive heart failure or severe cardiac disease is diagnostic for low-output heart failure.

NOTE: NONCARDIOGENIC ascites, pleural effusion, pulmonary edema, or peripheral edema can be found in patients that do not have heart failure. In these patients, PCWP and central venous pressure (CVP) will be normal and other diagnoses should be pursued.

CARDIOVASCULAR DISEASES THAT COMMONLY LEAD TO HEART FAILURE

The most common acquired heart diseases in dogs and cats that lead to heart failure are as follows:

- Chronic, acquired degeneration of the atrioventricular valves (common in dogs; rare in cats)
- Cardiomyopathy
  1. Dilated cardiomyopathy (common in dogs; rare in cats)
  2. Hypertrophic cardiomyopathy (common in cats; rare in dogs)
  3. Unclassified cardiomyopathies (cats)
  4. Restrictive cardiomyopathy (cats)
- Dirofilariasis and other causes of cor pulmonale (common in dogs; uncommon in cats)
- Pericardial disease or effusion (common in dogs, rarely clinically significant in cats)

- Rhythm and conduction abnormalities (dogs and cats)
- Hyperthyroid heart disease (cats)
- Hypertensive heart disease (dogs and cats)
- Bacterial endocarditis (dogs and cats)
- Cardiac tumors (common in dogs; rare in cats)

CHRONIC ACQUIRED DEGENERATIVE VALVULAR DISEASE

Definition

Chronic acquired degenerative valvular disease, sometimes called endocardiosis, is an idiopathic degenerative disease of the atrioventricular (AV) valves that leads to valvular insufficiency.

It is a common cause of cardiac disease in the dog, characterized by nodular thickening of the edges of the atrioventricular valves. (Blood DC, Studdert VP: Bailliere's Comprehensive Veterinary Dictionary, 2nd ed. A Baillière Tindall book. Philadelphia, WB Saunders, 1998.)

Pathology

The mitral and tricuspid valves are most commonly affected. A spectrum of AV valve lesions may be observed; however, the most common change is a shortening and thickening of the valves, leading to incompetency. Chordae tendineae often shorten, become thick and nodular, and may rupture. Histologic changes in the valve and chordae tendineae include proliferation of the spongiosa layer secondary to infiltration and increased deposition of an extracellular matrix material called glycosaminoglycans.

Pathologic consequences of chronic AV valve insufficiency include dilation and hypertrophy (volume overload hypertrophy) of the atria and ventricles, endocardial fibrosis of the atrium (jet lesions), and occasionally a full thickness left atrial tear.

Pathophysiology

The AV lesions result in an orifice where the valve leaflets would have normally met. The orifice permits regurgitation of blood from the ventricle into the atrium during ventricular contraction. For any given size of defect, the magnitude of blood regurgitating back across the mitral valve is greater than across the tricuspid valve because the left ventricle develops much greater force than the right ventricle does. Consequently, left heart failure resulting from mitral regurgitation is much more common than right heart failure resulting from tricuspid regurgitation.

The valvular leak initially leads to a decreased amount of blood pushed forward into the aorta. *At this stage, the reduced cardiac output is clinically significant only because of the compensatory mechanisms that it initiates, not because it is of sufficient magnitude to cause clinical signs in most patients.* The kidneys sense the decrease in systemic blood flow and retain sodium and water to increase blood volume in compensation. This increases venous return to the heart, which initially "stretches" the myocardium in the affected ventricle. The affected ventricle responds to this stretch by growing larger to increase the end-diastolic volume. As a result of this *eccentric (volume overload) hypertrophy,* the ventricle is able to pump a greater quantity of blood to compensate for blood lost through the valvular leak without a significant increase in the end-diastolic pressure within the ventricle, atria, pulmonary veins, or capillaries.

Typically, this condition worsens over time, with the ventricle growing larger as the mitral orifice enlarges and regurgitation worsens. The left atrium dilates to accommodate the increased amount of incoming systolic blood flow. Compensatory mechanisms maintain adequate forward blood flow without increasing left atrial (and therefore pulmonary capillary) pressure beyond that which can be compensated for by enhanced pulmonary lymphatic drainage, until the leak becomes severe and left atrial pressure increases to the point that pulmonary edema results.

Clinical consequences of advanced mitral valve insufficiency include elevated pulmonary venous pressure, pulmonary edema, left atrial enlargement with bronchial compression, supraventricular arrhythmias such as atrial premature contractions and atrial fibrillation, and, late in the course of the disease, ventricular myocardial dysfunction. The most common clinical signs associated with severe mitral regurgitation include exercise intolerance, coughing, and respiratory distress (dyspnea).

Because normal right ventricular systolic pressure is low (<30 mmHg), regurgitant flow across all but the most severe tricuspid valve lesions is not very large in magnitude, and congestive heart failure secondary to acquired, isolated, tricuspid regurgitation is less common. Consequences of tricuspid regurgitation are usually related to elevated systemic venous pressures, with hepatomegaly, ascites, and rarely subcutaneous edema. In many patients in which signs of right heart failure are identified, pulmonary hypertension is also present. Biventricular heart failure may manifest as pleural effusion.

Syncope can occur in advanced valvular heart disease and may be related to paroxysmal arrhythmias or vigorous coughing with reduced venous return. Syncope may occur in patients with no other clinical signs of heart failure.

Signalment

Degenerative AV valve disease affects a broad range of breeds and ages; however, this disease is most common in middle-aged or older small breed dogs.

For the forgoing reasons, clinical signs are more common in acquired left AV valve disease; therefore, the following discussion describes left AV valve myxomatous degeneration. Extrapolation to right AV valve myxomatous degeneration is straightforward.

Suggestive Diagnostic Findings

1. A systolic murmur over the left cardiac apex in a mature dog
2. Radiographic, echocardiographic, or electrocardiographic (ECG) evidence of left heart enlargement
3. Radiographic evidence of pulmonary venous distention or pulmonary edema

Definitive Diagnostic Criteria

1. Evidence of left ventricular volume overload hypertrophy and left atrial enlargement, thickened mitral valve leaflets, and normal to increased shortening fraction on an echocardiogram in conjunction with a typical left apical systolic murmur
2. Presence of a regurgitant jet across the mitral valve on spectral or color flow Doppler, in conjunction with criteria in #1
3. Regurgitation of radiopaque dye into the left atrium after dye injection into the left ventricle at the time of cardiac catheterization, in conjunction with criteria in #1

Differential Diagnoses

1. Previously unrecognized congenital malformation of the atrioventricular valve apparatus—e.g., mitral valve dysplasia—results in similar pathophysiology and clinical signs.
2. Bacterial endocarditis of the left AV valve—results in similar pathophysiology and clinical signs.
3. Dilated cardiomyopathy—may have similar clinical, electrocardiographic, and radiographic appearance.
4. Primary respiratory diseases, especially tracheal collapse, chronic bronchitis, and pulmonary fibrosis—may manifest with cough and exercise intolerance.
5. Neurologic and metabolic disorders—may result in episodes similar to syncope seen in some dogs with mitral insufficiency.

A. THE ASYMPTOMATIC PATIENT

History

No visible clinical signs of heart disease are present.

Physical Examination

Detection of a cardiac murmur during a routine examination is usually the first clue that valvular degeneration has begun. Cardiac findings are typically restricted to auscultation, which reveals a systolic murmur heard best over the left cardiac apex with mitral regurgitation or the tricuspid valve region with tricuspid regurgitation. Typically, the murmur is softer in the early stages of valve incompetency. It is common for the murmur to become louder and pansystolic as valvular regurgitation progresses. Although loud holosystolic and pansystolic murmurs are typical of more advanced disease, the severity of mitral regurgitation cannot be reliably predicted by auscultation alone.

Radiography

The thoracic radiograph during this stage may be normal or may show mild to moderate left atrial and left ventricular enlargement. Thoracic radiography is particularly valuable in following the progression of valvular incompetency and the cardiomegaly that develops with more advanced disease.

Electrocardiography

The ECG is usually normal in this stage, although P-wave abnormalities may occur, and evidence of left ventricular enlargement may become apparent if the disease has progressed to the moderate stage.

Echocardiography

The echocardiogram reveals no to moderate left atrial and left ventricular enlargement, depending on the severity of the disease. The mitral valve leaflets may appear thickened.

Therapeutic Recommendations (See Appendices B and C for specific medicaments and dosage recommendations)

In the absence of cardiac enlargement, there is no evidence that any therapy is indicated or beneficial.

Some Council members believe that in the presence of moderate to severe cardiomegaly, angiotensin converting enzyme (ACE) inhibitor therapy may be beneficial. Evidence is currently lacking in dogs. The Council will continue to review this issue as new data become available.

B. MILD TO MODERATE HEART FAILURE

Signs of heart failure are evident to the client and may be visible on presentation.

History

Client complaints generally include reports of episodic cough, exercise intolerance, lethargy, difficult breathing, tachypnea, and nocturnal restlessness.

Physical Examination

The dog may appear normal, particularly in the mildest phases of congestive heart failure. This is particularly true if coughing is caused by left main stem bronchial compression (not a sign of heart failure) and not by overt pulmonary edema. A systolic cardiac murmur is always present, usually loudest over the left apex. In many cases palpable precordial thrills associated with mitral and/or tricuspid regurgitation are evident. The cardiac rhythm may be regular or irregular. Isolated atrial premature complexes are common. More advanced arrhythmias may be anticipated in some dogs. The arterial pulse may be normal or brisk. Irregularities of the pulse are expected with cardiac arrhythmias. Congestive left heart failure is evident as exercise intolerance, tachypnea, and possible inspiratory and early expiratory crackles. (Caution: absence of these sounds does not rule out pulmonary edema, and presence of pulmonary crackles is more commonly identified in older dogs with primary lung disease.) A wheeze may be detected in dogs with compression of the left main stem bronchus by the left atrium. When tricuspid regurgitation is prominent, hepatomegaly and ascitic fluid accumulation may be noted.

Radiography

Cardiomegaly, which is usually left sided, is evident. Dorsal deviation of the trachea in dogs that are not flat chested and elevation and compression of the left main stem bronchus are common findings. Presence of left atrial and left auricular appendage enlargement is expected on both dorsoventral and lateral thoracic radiographs. Pulmonary edema is characterized most frequently by increased perihilar and caudodorsal lung densities.

Electrocardiography

The ECG rate and rhythm may be normal. Atrial premature complexes may be observed with progressive atrial distention. Ventricular extrasystoles may be observed but are less common than in dogs with dilated cardiomyopathy. Changes in the P waves are common and include widened P waves ("P mitrale") and increased amplitude P waves ("P pulmonale"). The frontal mean electrical axis is typically normal, but increased amplitude R waves are sometimes observed in leads II and a VF.

Echocardiography

Typical echocardiographic changes include moderate to severe left atrial enlargement, left ventricular volume overload (eccentric hypertrophy), and a hyperdynamic left ventricular motion (shortening fraction exceeding 40% and commonly >50%). Myocardial function is usually normal at this stage as evidenced by a normal end-systolic diameter. The increased shortening fraction is the result of the increase in end-diastolic diameter with a normal end-systolic diameter. Exuberant mitral valve excursion and thickening of the mitral valve leaflets are typical findings. Progressive mitral regurgitation is associated with increasing cardiac dimensions and left ventricular shortening fraction. Doppler echocardiography (spectral or color flow) may be used to document the presence of mitral regurgitation and may be useful in estimating the severity of the regurgitation.

Therapeutic Recommendations (See Appendices B and C for specific medicaments and dosage recommendations)

1. Diuretic
2. ACE inhibitor
3. Sodium-restricted diet, if tolerated by the patient
4. Digitalis glycoside: The Council could not reach a consensus regarding digitalis therapy for this class of canine patient.

C. ADVANCED HEART FAILURE

Clinical findings such as dyspnea at rest, markedly diminished exercise tolerance, alveolar pulmonary edema, cachexia, or obvious ascites are seen in patients with advanced congestive heart failure. Pallor of the mucous membranes secondary to low cardiac output and pronounced vasoconstriction *may* occur, although normal mucous membrane color and refill time do not rule out forward heart failure or systemic hypoperfusion.

History

Client complaints generally include reports of frequent cough, exercise intolerance, lethargy, difficult

breathing, tachypnea, and nocturnal restlessness. Owners may also report syncope.

Physical Examination

Unless heart failure results from a peracute incident, such as a chordal rupture, many dogs with advanced heart failure are in poor body condition and have experienced weight loss. Respiratory distress and tachypnea are typical clinical findings. In biventricular failure or right heart failure, the patient may have ascites. Systolic murmurs, as previously described, are present. The arterial pulse may be weak or normal and may be irregular because of premature depolarizations or atrial fibrillation. Dogs with respiratory distress may have crackles secondary to pulmonary edema but often have only increased bronchovesicular sounds secondary to hyperpnea. In advanced cases of right heart failure, there will be considerable ascites as well as hepatomegaly. Jugular venous pressure is often elevated, and jugular pulsations may be evident. Arrhythmias are very common in this phase, and atrial fibrillation is a frequent cause of deterioration in class from moderate to severe heart failure.

Note: Older small breed dogs are seen commonly with pulmonary crackles and a murmur of mitral regurgitation. Many of these dogs have primary respiratory disease rather than heart failure, and the finding of a heart murmur is incidental.

Radiography

In addition to radiographic abnormalities previously mentioned, alveolar infiltrates typical of cardiogenic pulmonary edema will be observed. These infiltrates are usually most evident in the hilar region but may be diffuse. Infiltrates are asymmetrical in some dogs, with the right side more dense than the left side. Cardiomegaly may be extreme and may mimic pericardial effusion in some dogs, although usually the markedly enlarged left atrium can be identified. Abdominal radiographs demonstrate hepatomegaly and may show fluid accumulation if right heart failure is also present.

Electrocardiography

In addition to the abnormalities mentioned in the previous section, cardiac arrhythmias are quite common. Atrial fibrillation is probably the most frequently encountered sustained cardiac arrhythmia. Ventricular tachyarrhythmias may also be observed.

Echocardiography

The mitral valve leaflets usually are markedly thickened, and there may be evidence of mitral valve prolapse or flail, which is evidence of chordae tendineae rupture. Severe left atrial and left ventricular enlargements are present at this stage. Global left ventricular function (shortening fraction) is usually well preserved, although myocardial contractility may actually be decreased in some dogs, especially large breed dogs, at this stage. In severe mitral regurgitation, decreased myocardial function is characterized by a normal or below normal shortening fraction, increased separation between the mitral valve opening point (E point) and ventricular septum, and an increased end-systolic diameter.

The increase in end-systolic diameter denotes the decrease in myocardial function seen in late stage mitral regurgitation, and the increase in end-diastolic diameter usually keeps the shortening fraction in the normal range or above.

Therapeutic Recommendations

THERAPY FOR ADVANCED HEART FAILURE—HOME CARE POSSIBLE (See Appendices B and C for specific medicaments and dosage recommendations)

1. Furosemide
2. ACE inhibitor
3. Digitalis glycoside
4. Hydralazine titration*
5. Addition of another class of diuretic

Possible use of the following:

1. Sodium restriction, if the dog will accept it
2. Antiarrhythmic therapy, if needed
3. Nitrates
4. Theophylline
5. Codeine or other cough suppressants

THERAPY FOR ADVANCED HEART FAILURE—HOSPITALIZATION MANDATORY FOR STABILIZATION (See Appendices B and C for specific medicaments and dosage recommendations)

1. Oxygen therapy
2. Intravenous furosemide or another loop diuretic*
3. Preload reduction with topical nitroglycerine or nitroprusside (blood pressure must be monitored if nitroprusside is used)
4. Afterload reduction with hydralazine or sodium nitroprusside to reduce mitral regurgitant fraction†

*In the presence of left main stem bronchial compression, refractory or progressive left-sided heart failure, or insufficient response to ACE inhibitor therapy, the addition of hydralazine should be considered. If added onto ACE inhibitor therapy, care must be taken not to induce profound hypotension. The drug should generally be titrated using blood pressure (systolic or mean) as the monitoring tool. A board-certified cardiac specialist should be consulted.

†Most effective at reducing life-threatening pulmonary edema.

5. Amrinone or milrinone infusion
6. Dobutamine
7. Morphine
8. Theophylline
9. Antiarrhythmic therapy (if needed)
10. Pleurocentesis (if needed)*

If ascitic fluid accumulation or pulmonary edema is refractory to therapy with one diuretic, a second diuretic can be added. Examples include hydrochlorothiazide or a combination of hydrochlorothiazide plus spironolactone. Also, the addition of hydralazine should be considered as outlined earlier in refractory left heart failure.

CANINE DILATED CARDIOMYOPATHY

Definition and Etiology

Dilated cardiomyopathy (DCM) is a condition in which myocardial disease results in decreased myocardial contractility (primary myocardial failure). Volume overload hypertrophy of one or both ventricles occurs to compensate for the myocardial failure.

Most cases of cardiomyopathy in dogs are idiopathic; however, a variety of definable conditions may lead to myocardial failure and produce clinical signs indistinguishable from idiopathic DCM. The likely site of the disease is subcellular, and in some cases dilated cardiomyopathy is reversible upon supplementation of a deficient nutrient. American cocker spaniels with DCM are taurine and possibly carnitine deficient and usually respond to supplementation. Other dogs with DCM belonging to breeds in which DCM is not prevalent may be similarly affected. Some large breed dogs are carnitine deficient and responsive to supplementation; this has been reported in a family of boxer dogs.

Pathology

Global volume overload hypertrophy of all four cardiac chambers is common and characterized by a marked increase in heart weight and chamber enlargement with wall thickness that is normal to thinner than normal. Endomyocardial fibrosis may be present, as well as dilation of the atrioventricular (AV) valve annuli. The AV valves are generally normal or show minimal degenerative change.

Histologic manifestations of idiopathic DCM include attenuated, thinned myocytes that appear "wavy" and separated. Myocardial degeneration, cytoplasmic vacuolization, necrosis, and fibrosis are usually seen, but the most remarkable finding usually is the vast amount of relatively normal appearing myocardium. Except in rare cases of myocarditis (e.g., Chagas' disease), inflammatory cells are sparse or absent.

*Most effective at reducing life-threatening pleural effusion.

Pathophysiology

Dilated cardiomyopathy occurs when a primary disease of the myocardium results in a decrease in myocardial contractility and causes idiopathic primary myocardial failure. This disease progresses insidiously over a number of years. In the early and middle stages of the disease, the dog appears normal, and the disease can usually only be identified by echocardiographic examination.

As a consequence of depressed myocardial contractility, end-systolic diameter and volume initially increase. The chamber eccentrically hypertrophies secondary to renal salt and water retention to increase end-diastolic diameter and volume. This allows the heart to compensate for the depression in contractility and to maintain a normal stroke volume at a normal end-diastolic intraventricular pressure. As the disease progresses, myocardial contractility is further depressed, and the heart grows larger.

At the end-stage of the disease, the ability of the heart to hypertrophy further becomes limited. The kidneys retain more sodium and water, and blood volume continues to increase without further chamber enlargement, resulting in increased ventricular diastolic pressure. This increase in diastolic pressure backs up into the atrium, veins, and capillary bed behind the affected ventricle, causing edema. When the ventricular size is increased, AV valvular regurgitation commonly occurs and further aggravates the increase in atrial, venous, and capillary pressures, although the amount of regurgitation is usually mild. Cardiac output may also become inadequate at this stage, resulting in clinical signs of hypoperfusion. Tachyarrhythmias, such as atrial fibrillation, may result in worsened hemodynamics and may promote further myocardial deterioration.

Signalment

Affected dogs are predominantly male, middle-aged to geriatric, and large or giant breeds, such as Doberman pinschers, Great Danes, Irish wolfhounds, and St. Bernards. Spaniels are a notable exception, as springer spaniels and cocker spaniels are sometimes affected with this disease. A wide range of age groups may be affected, including dogs as young as 6 months of age or older than 10 years of age.

Diagnostic Criteria for Dilated Cardiomyopathy

The echocardiogram is the gold standard for diagnosis of dilated cardiomyopathy. Ventricular chamber en-

largement with decreased ventricular shortening fraction is the feature most characteristic of this disorder.

A presumptive diagnosis of dilated cardiomyopathy can usually be made under the following conditions:

1. Identification of a predisposed breed (dilated cardiomyopathy is unusual in other breeds and mixed breeds)
2. Radiographic evidence of generalized cardiomegaly
3. Auscultation of a gallop sound (rhythm)
4. Demonstration of objective signs of congestive heart failure on physical examination and radiography
5. Evidence of cardiac arrhythmias: atrial fibrillation and ventricular tachyarrhythmias are most characteristic

In some breeds, ventricular tachyarrhythmias may precede echocardiographically recognizable reduction in myocardial function.

Differential Diagnoses

1. Previously unrecognized congenital heart disease, especially patent ductus arteriosus and mitral valve dysplasia*
2. Mitral regurgitation caused by degenerative valve disease in a large-breed dog*
3. Pericardial disease
4. Bacterial endocarditis
5. Primary cardiac arrhythmia
6. Severe endocrine deficiency, such as hypothyroidism, Addison's disease
7. Neurologic disease in the patient with syncope

A. THE ASYMPTOMATIC PATIENT

History

No visible clinical signs of disease are present.

Physical Examination

Serendipitous detection of a systolic heart murmur, which is usually soft, an audible third heart sound (gallop sound), or an arrhythmia should prompt consideration of occult cardiomyopathy. The detection of cardiomegaly during routine thoracic radiography or during evaluation of another condition may be an early clue to the presence of myocardial disease. Occasionally an affected dog is identified via echocardiographic screening.

*These differential diagnoses are most common and are often difficult to differentiate from DCM in later stages when myocardial failure may be a prominent component.

Radiography

The thoracic radiograph may be normal, or generalized mild to moderate cardiomegaly, most commonly left-sided, may be evident. Pulmonary venous distention may indicate incipient heart failure.

Electrocardiography

The ECG may be normal or demonstrate left heart enlargement, a ventricular conduction abnormality, or isolated atrial or ventricular premature complexes.

Echocardiography

End-systolic diameter is always increased because of the decrease in myocardial contractility. *End-diastolic diameter* is usually increased to compensate for the myocardial failure. When echocardiographic evidence of myocardial failure is present in the absence of clinical signs, the cardiac chambers are usually at or slightly above the upper limits of normal for end-diastolic diameter, and left ventricular shortening fraction (SF) is decreased to between 15% and 25% because of the increase in end-systolic diameter. However, a SF <15% is occasionally observed in asymptomatic patients.

Therapeutic Recommendations (See Appendices B and C for specific medicaments and dosage recommendations)

The Council could not reach a consensus regarding recommendations for treating asymptomatic canine patients with dilated cardiomyopathy.

Some members believe therapeutic intervention is appropriate at this stage. Others decline to recommend therapy at this point. Those Council members in favor of pharmacologic intervention in echocardiographically confirmed cases of dilated cardiomyopathy suggest one or both of the following medicaments: ACE inhibitors, digitalis.

Note: L-Carnitine and taurine can be supplemented if a deficiency is clearly documented. The benefits of supplementation of both nutrients have been demonstrated in American cocker spaniels with the disease.

B. MILD TO MODERATE HEART FAILURE

History

Signs of heart failure have become evident to the client at this stage and are often visible at the time of presentation. Common historical findings include dyspnea, cough, weight loss, exercise intolerance, lethargy, and depression. The onset of congestive left heart

failure is heralded by tachypnea and respiratory distress. Affected dogs may exhibit a mild or intermittent cough. Dogs with right heart failure commonly have ascites.

Physical Examination

Some dogs with mild to moderate heart failure resulting from dilated cardiomyopathy demonstrate significant weight loss. Careful auscultation usually indicates the presence of a gallop sound (rhythm) or a left apical systolic murmur. Cardiac rhythm abnormalities may be evident on auscultation and palpation of the femoral pulse. The arterial pulse is normal to hypokinetic. Jugular venous pressure is usually normal in mild heart failure but may become elevated with progression of disease. Congestive left heart failure is typical and is characterized on physical examination by an increased respiratory rate. End-inspiratory crackles are sometimes identified. Early signs of right heart failure include elevated jugular venous pressure, hepatomegaly, and mild ascites.

Radiography

Typical findings are left-sided or generalized cardiomegaly with left atrial enlargement, pulmonary venous distention, and increased pulmonary densities typical of pulmonary edema. A small pleural effusion may be evident. Hepatomegaly is a common finding on abdominal radiography.

Electrocardiography

Cardiac rhythm disturbances are common and include atrial premature complexes, ventricular premature complexes, paroxysmal ventricular tachycardia, and more sustained tachyarrhythmias. Atrial fibrillation may be evident in some dogs; in dogs with myocardial failure, the onset of atrial fibrillation commonly contributes to progression to more advanced stages of congestive heart failure. P waves may be widened, and alterations in the QRS morphology are expected. Other ECG changes may include increased amplitude R waves, widened QRS complexes, and slurring of the R wave descent. Nonspecific ST-segment and T-wave changes are also commonplace.

Echocardiography

Characteristic features are a marked increase in end-systolic diameter, with secondary left ventricular eccentric (volume overload) hypertrophy and moderately increased end-diastolic diameter, resulting in left ventricular hypokinesis (SF usually <15%), increased separation between the ventricular septum and the initial opening (E point) of the septal mitral leaflet, and varying degrees of regional left ventricular wall dysfunction. Variable and chaotic contraction of the ventricular walls is typical in patients with atrial fibrillation. Color flow Doppler echocardiography usually reveals a small mitral regurgitant jet. Ultrasound of the liver in patients with right heart failure demonstrates enlarged hepatic veins.

Therapeutic Recommendations (See Appendices B and C for specific medicaments and dosage recommendations)

1. Digitalis glycoside
2. Diuretic
3. ACE inhibitor
4. Antiarrhythmic therapy when indicated: digoxin, beta-blocker, diltiazem for atrial fibrillation; ventricular antiarrhythmic drugs for ventricular arrhythmias
5. Dietary sodium restriction, if tolerated
6. L-Carnitine or taurine may be supplemented when appropriately based on suitable laboratory tests. Both should be administered to American cocker spaniels with DCM
7. Low-dose beta-blocker*

C. ADVANCED HEART FAILURE

History

Most canine patients with DCM present with advanced heart failure. Disease onset often appears acute to the owner even though the disease has been progressing for years. Clinical findings such as dyspnea at rest, markedly diminished exercise tolerance, or abdominal distention are reported in patients with advanced congestive heart failure.

Physical Examination

Dogs with dilated cardiomyopathy in advanced heart failure are often cachectic, weak, lethargic, anorectic, and dyspneic. Dogs in cardiogenic shock from severe hypoperfusion may be moribund. Sinus tachycardia, atrial fibrillation, or sinus rhythm with premature ventricular complexes is usually detected. A gallop sound (rhythm) is a consistent finding but may be difficult to detect in arrhythmic patients and by untrained personnel. Systolic murmurs of mitral or tricuspid regurgitation may be heard. The arterial pulse may be hypoki-

*The Council could not reach a consensus regarding the efficacy and advisability of low-dose beta-blocker therapy. Beta-blockers are efficacious at improving myocardial function in some humans with dilated cardiomyopathy. There are no published studies of beta-blocker therapy in dogs with DCM, and pilot studies have not been encouraging.

netic and may be irregular because of a cardiac arrhythmia. Jugular venous distention may be detected.

Most dogs with advanced heart failure manifest signs of left or biventricular heart failure; usually respiratory distress and tachypnea resulting from pulmonary edema, pleural effusion, or both are evident.

Radiography

Cardiomegaly is usually moderate to severe, and the heart is usually globally enlarged. Cardiomegaly may be difficult to appreciate in some deep-chested dogs, especially in Doberman pinschers. Other common radiographic changes include pulmonary venous distention, alveolar lung infiltrates of pulmonary edema, and pleural effusion.

Electrocardiography

Previously described electrocardiographic abnormalities are expected. Atrial fibrillation or sinus rhythm with paroxysmal ventricular tachycardia is common at this stage.

Echocardiography

Previously described echocardiographic abnormalities are present but more severe. Moreover, pleural and small pericardial effusions secondary to heart failure may be seen.

Therapeutic Recommendations

Dilated cardiomyopathy is associated with a higher mortality rate than the other diseases that lead to heart failure. ACE inhibitors have been shown to prolong survival with dilated cardiomyopathy. Beta-blockers have been shown to prolong survival in other species with dilated cardiomyopathy; however, studies in dogs are lacking, and preliminary studies are discouraging.

Dogs with dilated cardiomyopathy die from heart failure or die suddenly, presumably from ventricular arrhythmia deteriorating into ventricular fibrillation. Effective therapy to prevent sudden death has not been elucidated in dogs. Therapy outlined here is for heart failure. Ventricular antiarrhythmics can be administered but are believed to be ineffective in preventing sudden death.

Advanced heart failure is subdivided therapeutically into two subclasses:

THERAPY FOR ADVANCED HEART FAILURE—HOME CARE IS POSSIBLE

(See Appendices B and C for specific medicaments and dosage recommendations)

1. Digitalis
2. Diuretic therapy
3. ACE inhibitor
4. Dietary sodium restriction, if accepted
5. Antiarrhythmic drug therapy, when appropriate, to control heart rate in atrial fibrillation (e.g., digoxin, diltiazem, beta-blocker) or when required to suppress ventricular ectopia (e.g., procainamide, tocainide, etc.)
6. No consensus was reached regarding the use of low-dose beta-blockade therapy in this stage of cardiomyopathy. There was a consensus, however, that beta-blockade was appropriate if used to control ventricular rate response in dogs with atrial fibrillation.
7. Taurine or carnitine supplementation, as described previously

Alternative therapies include the following:

8. Hydralazine
9. Nitrates
10. Bronchodilators, such as theophylline and related compounds

Note: Alternative therapy is generally added in stepwise fashion in those dogs for which additional drug therapy is warranted because of progressive signs of cardiac failure. Hydralazine is particularly likely to be helpful when there is concurrent moderate mitral regurgitation. However, combination vasodilator therapy may be associated with clinically significant hypotension and impaired renal perfusion. Blood pressure monitoring should be available. Consultation with a board-certified cardiologist is encouraged.

THERAPY FOR ADVANCED HEART FAILURE WHEN HOSPITALIZATION IS MANDATORY

(See Appendices B and C for specific medicaments and dosage recommendations)

1. Intravenous diuretic (furosemide* or another loop diuretic)
2. Dobutamine* or amrinone infusion
3. Oxygen
4. Preload reduction using nitroglycerine ointment or sodium nitroprusside* (arterial blood pressure must be monitored during sodium nitroprusside therapy).
5. Morphine
6. Theophylline may be beneficial but may aggravate cardiac arrhythmias

THERAPY FOR CARDIAC ARRHYTHMIAS

Cardiac arrhythmias are of particular concern in dogs with dilated cardiomyopathy, and antiarrhythmic

*These are the most effective drugs for controlling severe pulmonary edema.

drug therapy should be prescribed when arrhythmias are present.

Atrial arrhythmias, particularly atrial fibrillation:

1. Digoxin
2. Beta-blockers
3. Diltiazem

Note: Both diltiazem and beta-blockers depress myocardial contractility at higher dosages. In using these drugs to control ventricular rate response, a low initial starting dosage should be chosen, namely 0.1 to 0.2 mg/kg of body weight orally three times a day for propranolol and 0.5 mg/kg orally three times a day for diltiazem. Incremental doses should be used to gradually obtain the desired heart rate effect.

Ventricular arrhythmias

Isolated or periodic ventricular extrasystoles: No consensus was reached by the Council regarding the treatment of these isolated rhythm disturbances; however, the use of Holter monitoring or additional consultation was believed to be worthwhile.

Sustained ventricular arrhythmias:

1. Lidocaine
2. Procainamide
3. Tocainide
4. Mexiletine
5. Quinidine
6. Beta-adrenergic blockers

CANINE HEARTWORM DISEASE

Definition

Heartworm disease is the clinical manifestation of parasitism by *Dirofilaria immitis,* a filarial nematode. Adult nematodes injure the pulmonary vascular tree and the lung, leading to pulmonary artery injury and, in severe infections, pulmonary hypertension and pressure overload on the right ventricle. The heart and lung are usually the principal organs injured in advanced dirofilariasis.

Pathology

The presence of *Dirofilaria* adults injures the pulmonary arterial endothelium, resulting in swelling, altered intracellular junctions, and platelet and leukocyte activation. These activated cells release factors that stimulate collagen formation, intimal thickening and proliferation, and medial hypertrophy of the pulmonary arteries. Intimal smooth muscle cells proliferate and migrate toward the surface, producing villus proliferation from the pulmonary arterial surface.

Consequent to these changes, the pulmonary arteries enlarge and narrow. Pulmonary thromboemboli, presumably secondary to dead adult worms, and exuberant microvillus formation may produce blockage of blood flow through the pulmonary arteries.

Pulmonary parenchymal reactions also can occur in heartworm disease. Sequestration of microfilariae and reaction to sequestered microfilariae in the lung parenchyma can cause pneumonitis. The exact mechanisms of pulmonary injury are not fully elucidated, but pathologic findings include eosinophilic pneumonitis, pulmonary fibrosis as well as pulmonary thrombosis, and infarction secondary to worm death.

The severity of heartworm disease is often, but not always, related to the parasite burden. Dogs that are severely allergic to the parasites commonly have severe pulmonary arterial and pulmonary parenchymal disease and are commonly amicrofilaremic. In dogs with large numbers of adult parasites, retrograde migration of worms into the right atrium and tricuspid valve apparatus may occur, resulting in caval syndrome.

Pathophysiology

The presence of adult heartworms results in the aforementioned anatomic changes in affected pulmonary arteries. Changes include narrowing of the vascular lumina and limitation of pulmonary blood flow.

If pulmonary artery disease is severe, and especially if thromboemboli are present, pulmonary vascular resistance increases, resulting in significant pulmonary hypertension. Right heart enlargement (eccentric hypertrophy) and right heart failure may then ensue. Why the heart develops eccentric rather than the expected concentric hypertrophy is unresolved. Pulmonary parenchymal changes, which may lead to alveolar hypoxia, add a reversible aspect of vasoconstriction that further increases pulmonary vascular resistance. Dogs with advanced dirofilariasis show marked exercise intolerance and may develop congestive right heart failure.

Signalment

There are no age or breed predilections for heartworm disease; however, large breed, male dogs are more commonly affected, probably because they are frequently outdoors. The earliest signs of heartworm disease are not likely to be seen before 7 months of age because of the life cycle of *D. immitis.*

Diagnostic Criteria

1. Identification of circulating microfilariae of *D. immitis* in dogs older than 5 months of age; transplacental transfer of microfilariae is considered possible in younger dogs. Microfilariae must be differentiated from those of *Dipetalonema reconditum.*
2. A positive serologic test for adult heartworm anti-

gen, especially with typical signs or radiographic changes of heartworm disease
3. Clinical signs of exercise intolerance, coughing, or congestive right heart failure in conjunction with compatible radiographic changes (a heartworm antigen test is also recomended to verify the diagnosis)

Differential Diagnoses

1. Primary respiratory disorders, including infectious, parasitic, inflammatory, and neoplastic diseases
2. Pulmonary neoplasia—primary or metastatic
3. Other forms of cardiac disease, such as dilated cardiomyopathy, tricuspid valve malformation or degeneration, congenital heart disease, pericardial disease

A. THE ASYMPTOMATIC PATIENT

History

Diagnosis of asymptomatic dirofilariasis is most often made by a positive microfilaria test or positive antigen test during routine screening for heartworm disease.

Physical Examination

Usually no abnormalities are identified on physical examination.

Radiography

Thoracic radiographs may be normal or may show varying degrees of pulmonary artery enlargement, blunting, and tortuosity; and right heart enlargement.

Electrocardiography

The electrocardiogram is usually normal at this stage.

Echocardiography

The echocardiogram is usually normal at this stage, although mild right heart enlargement and main pulmonary artery enlargement may be identified.

Therapeutic Recommendations

As per the recommendations of the American Heartworm Society (see Appendix A for specific medicaments and dosage recommendations).

B. MILD TO ADVANCED HEART FAILURE

History

Client complaints usually include exercise intolerance, possible syncope, and loss of condition. Difficult breathing, tachypnea, and coughing are frequent signs if there are concurrent pulmonary parenchymal complications. The opportunity for frequent exposure to mosquitoes and a lax preventive program are obvious risk factors for development of advanced dirofilariasis.

Physical Examination

Clinical signs of advanced heartworm disease can be grouped into respiratory signs, cardiovascular signs, signs referable to caval syndrome, and signs secondary to other disorders occurring as a result of heartworm infestation. The last category includes renal disease, disseminated intravascular coagulopathy, anemia, and dysproteinemia.

Respiratory signs generally include tachypnea, dyspnea, and coughing. Hemoptysis is seen occasionally and is probably related to rupture and hemorrhage of bronchial or pulmonary arteries into the lung parenchyma. These signs are the result of heartworm infestation, not of heart failure. Cardiovascular signs that are related to pulmonary vascular changes and pulmonary hypertension include weakness, which is often episodic, exercise intolerance, syncope, and clinical signs of congestive right heart failure.

Dogs with advanced heartworm disease usually show weight loss and a poor hair coat. Cardiac auscultation may demonstrate a normal heart rhythm or occasionally premature beats or even atrial fibrillation. The second heart sound may be normal, louder than normal, or split, the latter as a consequence of pulmonary hypertension. A systolic murmur of tricuspid regurgitation may be evident over the right hemithorax.

The arterial pulse is usually normal but central venous pressure is increased when heart failure has occurred. Jugular vein distention and pulsations are common in advanced dirofilariasis. Auscultation of the lungs may demonstrate increased bronchial sounds or crackles if there is pulmonary parenchymal reaction to the parasite or substantial pulmonary thromboembolism. Clinical signs of congestive right heart failure include hepatomegaly and ascites.

Radiography

Radiographic changes include right ventricular and possibly right atrial enlargement. Increased size of the main pulmonary artery commonly occurs. In advanced cases, a reversed "D" configuration to the cardiac silhouette is evident. Lobar pulmonary arteries become dilated, tortuous, and blunted, which is known

as pruning of the arteries. These changes are typically most severe in the caudal lobar arteries. Increased lung densities are often evident and may be related to noncardiogenic edema, eosinophilic infiltrates, pulmonary embolism and infarction, or pulmonary fibrosis.

Electrocardiography

The ECG is often normal in heartworm disease; however, with pulmonary hypertension sufficient to cause right heart failure, changes in the P waves and QRS complexes may occur. Interestingly, P pulmonale (increased P-wave voltage) is relatively uncommon in heartworm disease; however, widening of the P wave may be an indication of right atrial enlargement or conduction delay. An axis deviation to the right, characterized by prominent S waves in leads I, II, III, aVF, and the lower left chest leads, is commonly observed in dogs with severe right ventricular enlargement, right heart failure, or both. Rhythm disturbances ranging from sinus tachycardia to more profound irregularities, including right ventricular extrasystoles and atrial fibrillation, may be present.

Echocardiography

Echocardiography can be used to document enlargement of the right ventricle. However, echocardiography is most useful in dogs with caval syndrome, in which masses of heartworms can be readily identified in the tricuspid valve orifice, or in some dogs with occult dirofilariasis, in which adult heartworms may be visible in the pulmonary arteries by high quality, two-dimensional echocardiograms. Echocardiography may attain greater prominence with the use of flexible alligator forceps to manually remove heartworms from the pulmonary arteries.

Echocardiographic manifestations of advanced heartworm disease leading to right heart failure include right atrial, right ventricular, and pulmonary artery dilation. Flattening and abnormal motion of the ventricular septum is typical of right ventricular pressure or volume overload. Linear echogenic densities compatible with adult heartworms may be evident in the main pulmonary artery or occasionally in the heart chambers. Left ventricular contractility is typically preserved, but the left ventricular luminal dimensions may be decreased, resulting in decreased shortening fraction.

Therapeutic Recommendations (See Appendices B and C for specific medicaments and dosage recommendations)

1. Diuretic—maintenance therapy with a loop diuretic such as furosemide is recommended as initial treatment for congestive heart failure. The Council recommends the administration of a second diuretic, such as hydrochlorothiazide or hydrochlorothiazide plus spironolactone, or triamterene, in the event of refractory ascites. Malabsorption of orally administered diuretics is possible, and parenteral administration of loop diuretics may be more effective in some patients.
2. Cage rest is essential in dogs with heart failure caused by dirofilariasis. Benefits of cage rest include improved mobilization of edema and possibly increased patient survival following adulticide administration.
3. Digitalis glycosides—the use of digitalis glycosides is controversial in this setting. Some members of the Council believe these drugs may be effective and safe provided serum digoxin concentration is carefully monitored and conservative dosages are administered initially.
4. Aspirin—although aspirin is commonly recommended to reduce pulmonary vascular reaction, no consensus was reached by the Council regarding its efficacy. Strict attention must be directed to the possible development of gastric ulceration when aspirin is prescribed.
5. Antiarrhythmic—occasionally antiarrhythmic drug therapy is required to manage arrhythmias associated with heartworm disease.
6. ACE inhibitor—the benefits of ACE inhibitor therapy in left-sided and biventricular heart failure have been documented, but the benefits in isolated right heart failure caused by pulmonary hypertension have not been studied. For this reason, the Council recommends careful monitoring of any patient receiving this form of therapy.
7. Thiacetarsemide—administration should be attempted if and when heart failure is stabilized. Successful adulticide therapy may result in significant regression of pulmonary hypertension and, consequently, regression of signs of heart failure.

FELINE HYPERTROPHIC CARDIOMYOPATHY

Definition

Feline hypertrophic cardiomyopathy is an idiopathic myocardial disorder characterized by primary, and inappropriate, concentric hypertrophy of the left ventricle. Feline hypertrophic cardiomyopathy is a diagnosis of exclusion. Potential causes of secondary left ventricular concentric hypertrophy in cats include hyperthyroid heart disease, systemic hypertension, acromegaly, congenital subaortic stenosis, and congenital aortic stenosis.

Pathology

Left ventricular concentric hypertrophy is the classic feature of feline hypertrophic cardiomyopathy. The ventricular free wall and/or ventricular septum may be hypertrophied. Papillary muscle thickening is common. In some cats, the left ventricular outflow tract appears narrowed as a consequence of septal hypertrophy adjacent to the septal mitral leaflet.

Histologically, myocardial hypertrophy is the primary abnormality. Disorganization of myocytes is commonly observed. Interstitial and interfibral fibrosis may occur. Sclerosis and narrowing of intramural coronary arteries is a frequent microscopic feature. The left atrium is commonly distended and also hypertrophied, and thrombi may be observed in this chamber or remote to the heart. A frequent complication is a distant thromboembolus, which typically lodges at the aortic trifurcation (i.e., a saddle thromboembolus).

Pathophysiology

Hypertrophic cardiomyopathy is characterized by diastolic dysfunction of the left ventricle. As a consequence of many factors, including gross hypertrophy of the wall, myocardial fibrosis, and possibly insufficient coronary perfusion, the left ventricle becomes stiff and less distensible. Elevated left atrial pressure is required to fill the ventricle, leading to dilation and hypertrophy of the left atrium. Chronic elevations in left ventricular diastolic pressure are translated into the pulmonary vascular tree, leading to pulmonary venous congestion and edema.

The two major syndromes recognized in cats with feline hypertrophic cardiomyopathy are congestive heart failure and aortic thromboembolism. Stresses that lead to tachycardia may abruptly increase left ventricular stiffness by increasing myocardial oxygen demand. Functional abnormalities of relaxation may ensue, which further impair ventricular filling. This may explain the development of acute pulmonary edema in cats that were previously well compensated for their disease during clinical examinations and procedures.

Additional functional abnormalities may develop during systole. Mitral regurgitation is common in cats with hypertrophic cardiomyopathy and may be explained either by geometric changes in the left ventricle and papillary muscles or by systolic anterior motion of the mitral valve during systole. Movement of the anterior (septal) mitral valve toward the ventricular septum in systole may be associated with narrowing of the left ventricular outlet, generation of a pressure gradient, and a functional outflow obstruction. The overall significance of outflow obstruction in this disease is unresolved at this time.

Signalment

The age range of affected cats is very broad. Males are affected more commonly than females. Domestic short-hair cats, followed by domestic long-hair cats, appear to be most frequently affected. A genetic form of the disease occurs in Maine coon cats and may be present in other breeds as well.

Diagnostic Criteria

1. Hypertrophic cardiomyopathy should be a ruleout whenever the following are identified: cardiomegaly (especially left atrial enlargement), a gallop sound (rhythm), a systolic murmur, arterial thromboembolism, or congestive left heart failure. Definitive diagnosis of hypertrophic cardiomyopathy is based on either echocardiographic or angiographic evidence of left ventricular hypertrophy. However, other known causes of left ventricular hypertrophy must be excluded before this diagnosis is made.
2. Echocardiographic evidence of left ventricular hypertrophy, generally associated with left atrial enlargement, is sufficient evidence of hypertrophic cardiomyopathy in the absence of other causes of ventricular hypertrophy.
3. Selective or nonselective angiography may be used to demonstrate left ventricular hypertrophy; however, these techniques are invasive and are not recommended when echocardiography is available.

Differential Diagnoses

1. Other forms of cardiomyopathy: restrictive, dilated
2. Myocarditis
3. Hyperthyroidism
4. Hypertensive heart disease
5. Acquired valvular disease
6. Congenital heart disease

A. THE ASYMPTOMATIC PATIENT

History

The diagnosis is most commonly made after the serendipitous detection of a systolic cardiac murmur or gallop sound (rhythm) during the course of a clinical examination. Cardiomegaly may be detected when thoracic radiography is undertaken for another reason. Other affected cats may be identified because of echocardiographic screening for the disease.

Physical Examination

The most frequent clinical finding in an asymptomatic cat is a left apical or sternal border systolic murmur or a gallop sound (rhythm).

Radiography

Thoracic radiographs may appear normal or may show evidence of left atrial or left ventricular enlargement. No pulmonary edema is present.

Electrocardiography

The ECG may be normal or may show evidence of left ventricular enlargement or left axis deviation.

Echocardiography

The diagnosis of hypertrophic cardiomyopathy is based on echocardiography. Echocardiographic changes can range from mild, diffuse, or focal left ventricular wall thickening to severe left ventricular wall thickening with or without mild left atrial enlargement.

Therapeutic Recommendations (See Appendices B and C for specific medicaments and dosage recommendations)

1. Diltiazem or a beta-blocker. The Council could not reach a consensus; however, many members believe that one of these two medicaments should be prescribed.
2. Aspirin, administered orally every third day. The Council could not reach a consensus of opinion regarding the efficacy of this therapy.

B. MILD TO MODERATE HEART FAILURE

History

Clinical signs of mild to moderate heart failure generally include tachypnea, exertional dyspnea, and nonspecific signs of anorexia, listlessness, or rarely coughing. Coughing is usually mistaken for vomiting by the owner. Decreased activity may be a clinical sign but is difficult to document in cats. Some cats with hypertrophic cardiomyopathy may be affected by aortic thromboembolism, with minimal to no signs of congestive heart failure.

Physical Examination

Cats with heart failure, unlike dogs with heart failure, often maintain body condition. Many cats have abnormal cardiac auscultation that is characterized by either sinus tachycardia, the presence of occasional premature beats, a systolic murmur near the left apex and along the sternal border, or a gallop sound (rhythm). Arterial pulses are usually normal unless there is an aortic thromboembolus. The jugular venous pressure is usually normal. Cats with left heart failure rarely cough, although they may cough with tracheal palpation in the examining room. Most demonstrate tachypnea. Auscultation of the lungs may reveal fine inspiratory crackles related to pulmonary edema or simply harsh bronchovesicular sounds.

If an aortic thromboembolus is present, typical vascular, musculoskeletal, and neurologic deficits will be evident. These include cold limbs, absent or very weak pulses, paresis, contracture of affected muscle groups, pain, and progressive lower motor neuron neuropathy.

Radiography

Cardiomegaly is evident and is often more easily detected on the dorsoventral view, on which enlargement of the left auricle will be most prominent. Generally, there is mild elongation of the cardiac silhouette compatible with left ventricular hypertrophy. Pulmonary edema is evident as an increased interstitial or alveolar pattern and is frequently patchy and focal in appearance. Perihilar lung edema is not a common feature of congestive heart failure in cats, unlike the case in dogs.

Electrocardiography

A wide variety of ECG abnormalities have been detected in this disease. In some cats the ECG is normal. Other cats manifest increased amplitude or duration P waves, compatible with atrial enlargement. Increased amplitude R waves or a left cranial axis deviation may be observed. Increased duration of the QRS complex also may be recognized.

Echocardiography

This modality is the most accurate technique for diagnosing hypertrophic cardiomyopathy and is also helpful in assessing the severity of disease. Typical echocardiographic findings include ventricular septal, left ventricular wall, and papillary muscle hypertrophy. Left ventricular luminal size is commonly decreased when global hypertrophy is severe. The left atrium is enlarged in symptomatic cats. The shortening fraction is usually normal to elevated. Abnormal systolic motion of the septal (anterior) mitral leaflet may be observed, particularly in cats with a narrowed left ventricular outflow tract. Thrombi may occasionally be identified in the left atrium or left atrial appendage.

Therapeutic Recommendations (See Appendices B and C for specific medicaments and dosage recommendations)

1. Furosemide
2. Minimize stress

3. Diltiazem or beta-blocker. The Council could not reach a consensus regarding the superiority of one of these treatments over the other. (Note: The use of nonspecific beta-blockers should be avoided in the presence of pulmonary edema. Beta-blockers may be prescribed, however, following resolution of pulmonary edema.)
4. Nitrates—may be beneficial as supplemental treatment for pulmonary edema or if the cat is resistant to oral administration of medicaments.
5. Antiarryhythmic therapy—if an abnormal cardiac rhythm is identified and is sustained
6. Dietary sodium restriction, if tolerated

C. ADVANCED HEART FAILURE

Cats in this category demonstrate obvious signs of congestive heart failure, typically respiratory distress. Respiratory distress can usually be traced to the presence of alveolar pulmonary edema and occasionally pleural effusion, or both.

Special caution should be taken when evaluating and treating these cats as even minor restraint or manipulation can lead to marked exacerbation of respiratory distress and death. Many members of the Council emphasized that diagnostic tests should, in most cases, be delayed until symptomatic relief has been provided by oxygen and diuretic therapy and pleurocentesis, if significant pleural effusion is present.

History

Severe dyspnea at rest is the predominant clinical sign in most cats with advanced heart failure.

Physical Examination

The physical findings of advanced heart failure in cats are an extension of those noted in the previous section. Severe pulmonary edema manifests as dyspnea, tachypnea, cyanosis, and possibly pulmonary crackles. If pleural effusion is present, there may be evidence of a pleural fluid line, muffling of heart sounds, or dullness to percussion. Signs of thromboembolism are evident in some cats. A systolic murmur or gallop sound (rhythm) is usually evident, and sinus tachycardia, premature beats, or atrial fibrillation may be identified.

Electrocardiography

Electrocardiographic findings are the same as in cats with mild to moderate failure. In addition, there is a greater tendency toward atrial and ventricular arrhythmias. Cats with massive left atrial dilation may develop atrial fibrillation, which is poorly tolerated in cats with this disease.

Radiography

Radiography demonstrates cardiomegaly, which may be more generalized. There is usually marked left atrial and auricular appendage enlargement. Diffuse or patchy alveolar infiltrates of pulmonary edema or pleural effusion are evident.

Echocardiography

The echocardiographic features are those discussed in the previous section. Left atrial enlargement is often more severe.

Therapeutic Recommendations (See Appendices B and C for specific medicaments and dosage recommendations)

As a general rule, the hospital and home care of cats with hypertrophic cardiomyopathy and severe congestive heart failure are qualitatively similar.

1. Oxygen
2. Diltiazem and possibly a beta-blocker. The Council generally agreed that diltiazem was preferable to a beta-blocker in this setting.
3. Furosemide
4. Nitrate or ACE inhibitor, or both
5. Thoracocentesis if pleural effusion is present
6. Referral if the patient is persistently difficult to manage

Appendix B

Common Cardiovascular Drugs and Recommended Dosages Suggested by the International Cardiac Health Council

DISCLAIMER: The dosage ranges listed in this document are recommendations of the Council at the time this document was prepared. Primary responsibility for decisions regarding treatment of patients remains with the attending clinician. All patients should be carefully monitored for desirèd efficacious and undesired toxic effects during the institution, titration, and maintenance of therapy.

Drugs are listed in alphabetical order by general classification. The order of presentation in no way reflects the Council's preference for use. General recommendations for therapy may be found in the main body of this document. Knowledge of specific indications and contraindications is the responsibility of the attending clinician.

Drug (Trade Name)	*Species*	*Route*	*Dose*
Angiotensin-Converting Enzyme Inhibitors			
Captopril (Capoten)	Both	PO	0.5–2 mg/kg q8h
Enalapril (Enacard)	Dog	PO	0.5 mg/kg q12–24h
Enalapril (Enacard)	Cat	PO	0.5 mg/kg q12–72h
Beta-Adrenergic Blockers			
Atenolol (Tenormin)	Cat	PO	6.25–12.5 mg q12–24h (total dose; start low; titrate)
Esmolol (Brevibloc)	Both	IV	0.25–0.5 mg/kg, iv slow bolus; 50–200 μg/kg/min infusion
Propranolol (Inderal)	Dog	PO	0.1–2 mg/kg q8h (start low, titrate to effect in atrial fibrillation; higher doses used for other arrhythmias)
Propranolol (Inderal)	Cat	PO	2.5–5 mg q8h (total dose; start low; titrate)
Propranolol (Inderal)	Both	IV	0.01–0.1 mg/kg (start low; titrate to effect for supraventricular tachyarrhythmias)
Calcium Channel Blockers			
Diltiazem (Cardizem)	Dog	PO	0.5–1.5 mg/kg q8h (start low; titrate to effect for atrial fibrillation)
Diltiazem (Cardizem)	Cat	PO	7.5 mg q8h (total dose)
Verapamil (various)	Dog	IV	0.05 mg/kg (slow iv over 2–3 min; repeat same dose to effect up to a total dose of 0.15 mg/kg over 15–30 min for supraventricular tachycardia)
Diuretics			
Furosemide (Lasix)	Both	PO	1–4 mg/kg q8–24h, depending on need
Furosemide (Lasix)	Dog	IV	2–8 mg/kg q1–6h (short-term emergency therapy)
Hydrochlorothiazide (various)	Dog	PO	2–4 mg/kg q12h
Spironolactone (various)	Dog	PO	1–2 mg/kg q12–24h

Table continued on following page

Drug (Trade Name)	*Species*	*Route*	*Dose*
Positive Chronotropes			
Atropine (various)	Both	IV, IM, SC	0.02–0.04 mg/kg (as needed)
Glycopyrrolate (Robinul)	Both	IV, IM, SC	0.005–0.01 mg/kg (as needed)
Isoproterenol (various)	Both	IV	0.01–0.1 μg/kg/min constant rate infusion: 1 mg diluted into 500 ml of 5% dextrose or lactated Ringer's solution and infuse to desired effect
Positive Inotropes			
Amrinone (Inocor)	Dog	IV	1–3 mg/kg (bolus), 10–100 μg/kg/min (constant rate infusion; start low; titrate)
Digitoxin (Crystodigin)	Dog	PO	0.02–0.03 mg/kg q8h
*Digoxin (Lan-/Cardoxin)	Dog	PO	Dog (< 15 kg): 0.006–0.011 mg/kg q12h Dog (> 15 kg): 0.22 mg/m^2 body surface area q12h
*Digoxin (Lanoxin)	Dog	IV	0.0025 mg/kg q1h × 4 h (total 0.01 mg/kg)
*Digoxin (Lan-/Cardoxin)	Cat	PO	Cat (2–3 kg): 1/4 of a 0.125-mg tab q48h Cat (4–6 kg): 1/4 of a 0.125-mg tab q24h Cat (> 6 kg): 1/4 of a 0.125-mg tab q12h
Dobutamine (Dobutrex)	Dog	IV	2.5–20 μg/kg/min (constant rate infusion)
Dobutamine (Dobutrex)	Cat	IV	2–10 μg/kg/min (constant rate infusion)
Dopamine (Intropin)	Dog	IV	2.5–15 μg/kg/min (constant rate infusion)
Dopamine (Intropin)	Cat	IV	2–10 μg/kg/min (constant rate infusion)
Vasodilators			
Hydralazine (Apresoline)	Dog	PO	0.5–3 mg/kg q12h (start low; titrate)
Nitroglycerin ointment (various)	Dog	Topical	4–15 mg q6–12h (1 inch = 15 mg)
Nitroglycerin ointment (various)	Cat	Topical	3–4 mg q6–12h
Nitroprusside (Nipride)	Dog	IV	0.5–10 μg/kg/min (constant rate infusion)
Prazosin (Minipress)	Dog	PO	Dog (small): 0.5–1.0 mg q8h; begin with 0.5 mg Dog (medium to large): 1.0–2.0 mg q8h; begin with 1.0 mg
Ventricular Antiarrhythmics			
Amiodarone (Cordarone)	Dog	PO	loading dose: 10–20 mg/kg q24h × 7–10 days maintenance dose: 3–10 mg/kg q24h
Esmolol (Brevibloc)	Dog	IV	0.25–0.5 mg/kg, iv slow bolus; 50–200 μg/kg/min infusion
Lidocaine (Xylocaine)	Dog	IV	2–6 mg/kg slow bolus; 40–100 μg/kg/min infusion
Mexiletine (Mexitil)	Dog	PO	5–8 mg/kg q8h
Phenytoin (Dilantin)	Dog	PO	20–35 mg/kg q8h
Procainamide (Pronestyl)	Dog	IV, IM	5–15 mg/kg slowly q6h
Procainamide (Pronestyl)	Dog	PO	10–30 mg/kg q6–8h
Quinidine (various)	Dog	PO, IM	6–16 mg/kg q6–8h
Tocainide (Tonocard)	Dog	PO	5–20 mg/kg q8h

*Monitoring serum digoxin concentration at appropriate time intervals after dosing is recommended as a guide to maintaining therapeutic concentrations while reducing the probability of toxicity. Serum concentrations between 0.5 and 2.0 ng/ml sampled 6 to 8 hours after the last dose are the commonly quoted normal ranges. Consult your clinical laboratory for recommended protocols and desired serum concentration ranges.

ANCILLARY DRUGS COMMONLY USED CONCURRENTLY WITH CARDIOVASCULAR DRUGS AND DOSAGES

Drug (Trade Name)	*Species*	*Route*	*Dose*
Anticoagulant/Antiplatelet			
Aspirin (various)	Dog	PO	5–10 mg/kg q24–48h
Aspirin (various)	Cat	PO	80 mg q48–72h
Cough Suppressants and Bronchodilators			
Butorphanol (Torbutrol, Torbugesic)	Dog	PO	0.55 mg/kg q6–12h
Codeine (various)	Dog	PO	0.1–0.3 mg/kg q6–8h
Hydrocodone bitartrate (Hycodan)	Dog	PO	2.5–5 mg PO q6–24h (total dose)
Theophylline/aminophylline (various)	Dog	PO	5–10 mg/kg q8h

Drug (Trade Name)	Species	Route	Dose
Heartworm Adulticide			
Thiacetarsamide (Caparsolate)	Dog	IV	2.2 mg/kg twice daily for 2 days
Sedative/Analgesics			
Morphine (various)	Dog	IV	0.1 mg/kg q2min to effect (up to 1.0 mg/kg); repeat total dose q6h
Morphine (various)	Dog	SC, IM	0.5–1.0 mg/kg (as needed)
Morphine (various)	Cat	SC, IM	0.05–0.1 mg/kg (as needed)
Oxymorphone (Numorphan)	Cat	SC, IM	0.02–0.06 mg/kg (as needed)

The International Small Animal Cardiac Health Council, 1994.

THERAPEUTIC STRATEGIES FOR CONGESTIVE HEART FAILURE IN THE DOG: OPINION POLE FROM THE 8th INTERNATIONAL CARDIAC HEALTH COUNCIL*†

Heart Failure Severity‡	Low Salt Diet	Furosemide	Angiotensin-Converting Enzyme (ACE) Inhibitor	Digoxin	β-adrenergic Blocker or Diltiazem
No cardiac enlargement	0	0	+	0	0
Moderate-severe left atrial enlargement (LAE)	0	0	+ + +	+	0
Moderate-severe LAE plus: pulmonary venous congestion ± mild pulmonary edema	+ + + +	+ +	+ + + +	+	0
Moderate-severe LAE plus: moderate pulmonary edema					
A) Atrial fibrillation absent	+ + + +	+ + +	+ + + +	+ +	0
B) Atrial fibrillation present	+ + + +	+ + +	+ + + +	+ + + +	+ + + +
Moderate-severe LAE plus: severe pulmonary edema					
A) Atrial fibrillation absent	+ + + +	+ + + +	+ + + +	+ + +	0
B) Atrial fibrillation present	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +

*San Diego, California, 1998. Members in attendance included Clark Atkins, Claudio Bussadori, Philip Fox, Virginia Luis-Fuentes, Robert Hamlin, Bruce Keene, Mark Kittleson, Clarence Kvart, Linda Lemkuhl, Matt Miller, Kate Meurs, Takao Minami, Sydney Moïse, Yoshito Wakao.

†Degee of Consensus to Treat: 0, Zero concurrence; +, 15–38% Council concurrence; + +, 61% Council concurrence; + + +, 76–92% Council concurrence; + + + +, 100% Council concurrence.

‡Endocardiosis or dilated cardiomyopathy.

Appendix C

Cardiovascular Drugs—Dosages, Formulations, Indications, Side Effects: Recommendations Suggested by Fox PR, Sisson D, and Moïse NS

Drug	Trade Names, Formulations*	Approximate Dosage†	Category	Major Indications	Major Side Effects	Comments
Adenosine	Adenocard	Dog: 1–3 mg rapid IV bolus	Antiarrhythmic	Supraventricular tachycardias	Nausea, bradycardia, heart block, bronchoconstriction	
Albuterol	Proventil, Ventolin 2, 4 mg tablets 2 mg/5 ml syrup	Dog, Cat: 0.02–0.05 mg/kg bid-tid PO	Bronchodilator, selective β_2-adrenergic agonist	Bronchodilation, bradycardia	Tachycardia, tremors, restlessness, vomiting, anorexia	
Aminophylline	Various 100, 200 mg tablets 25 mg/ml injectable	Dog: 8–11 mg/kg tid-qid IV, IM, PO Cat: 4–5 mg/kg (approx 25 mg) bid PO	Bronchodilator, competitive inhibitor of phosphodiesterase	Bronchodilation	Tachycardia, tachypnea, anxiousness, depression, vomiting, diarrhea, anorexia	
Amiodarone	Cordarone 200 mg tablets	Dog: 10–20 mg/kg sid PO for 7–10 days (loading dose) 3–15 mg/kg sid, or 5 mg/kg eod PO (maintenance dose)	Complex antiarrhythmic (class I, II, III, IV activity, potassium channel blocker)	Difficult to control supraventricular or ventricular arrhythmias	Hepatotoxicity, anorexia, bradycardia, AV block, depression, negative inotropic effect; extensive list of side effects in humans	
Amlodipine besylate	Norvasc 2.5, 5 mg tablets	Dog: 0.05–0.1 mg/kg sid-bid PO Cat: 0.625 mg sid-bid PO	Calcium channel blocker (dihydropyridine)	Arterial hypertension	Hypotension	
Amrinone lactate	Inocor lactate 5 mg/ml injectable	Dog: 1–3 mg/kg slow IV bolus; 10–100 μg/kg/min CRI (start low, titrate to effect)	Phosphodiesterase inhibitor, positive inotrope, vasodilator	Severe myocardial failure	Hypotension, cardiac arrhythmias, hepatotoxicity, vomiting, anorexia	
Aspirin	Various 81, 325 mg tablets	Dog: 5–20 mg/kg sid-eod PO Cat: 25 mg/kg q3days PO	Antiplatelet aggregation	Prevent or reduce thromboembolism	Vomiting, gastrointestinal ulceration, bleeding	Buffered preparations administered with food may decrease gastrointestinal complications.
Atenolol	Tenormin 25, 50, 100 mg tablets 25 mg/ml oral suspension 0.5 mg/ml, 10 ml ampules injectable	Dog: 6.25–25 mg sid-bid, or 0.25–1 mg/kg sid-bid PO Cat: 6.25–12.5 mg sid-bid PO	Selective β_1-adrenergic blocker	Tachycardia, arrhythmias, arterial hypertension, diastolic dysfunction (e.g., HCM)	Sinus bradycardia, AV block, negative inotropic effect, weakness, depression, hypotension	Response to β-adrenergic blockade can be variable and depends upon the patient's level of sympathetic tone and underlying disease. When planning to discontinue, taper dosage—do not stop abruptly.

* The brands listed here do not include specific product endorsement but are intended to serve as a reference only. Frequently, additional commercial products or generic agents are available.

† This table suggests approximate dosages. Safe and effective doses may vary widely between patients, and therefore all dosages should ultimately be individualized. Always read manufacturer's recommendations.

Abbreviations: ACT, activated clotting time; AV, atrioventricular; bid, every 12 hours; CHF, congestive heart failure; CRI, constant rate infusion; eod, every other day; HCM, hypertrophic cardiomyopathy; IM, intramuscular; INR, international normalization ratio; ISI, international sensitivity index (the index of sensitivity of the thromboplastin reagent); IV, intravenous; PO, per os (orally); PTT, partial thromboplastin time; qid, every 6 hours; SC, subcutaneous; sid, every 24 hours; SR, sustained release; TD, transdermal; tid, every 8 hours.

Note: Antihypertensive dosages of angiotensin-converting enzyme inhibitors, β-adrenergic blockers, and diuretics may be higher than those that are indicated above for treatment of heart failure.

Atropine sulfate	Various 0.1 mg/ml injectable	Dog, Cat: 0.01–0.04 mg/kg IV, IM, SC	Anticholinergic, antimuscarinic	Bradycardia, advanced AV block	Tachycardia, transient AV block, constipation, dry mucous membranes, ileus	Do not combine with alkaline solutions.
Benazepril	Lotensin 5, 10, 20, 40 mg tablets Fortekor	Dog, Cat: 0.25–0.5 mg/kg sid-bid PO	Angiotensin-converting enzyme inhibitor	Congestive heart failure, arterial hypertension	Hypotension	
Bretylium tosylate	Bretylol 50 mg/ml, 10 ml vial injectable	Dog: 2–10 mg/kg IV	Antiarrhythmic (class III), antifibrillatory	Prevent ventricular fibrillation	Tachycardia, proarrhythmic, vomiting, hypotension	
Bumetanide	Bumex 0.5, 1, 2 mg tablets 0.25 mg/ml injectable	Dog: 0.03–0.06 mg/kg sid-bid PO	Loop diuretic	Congestive heart failure	Hypovolemia, electrolyte depletion, acid-base disturbances, azotemia	
Butorphanol tartrate	Torbutrol 1, 5, 10 mg tablets Torbugesic 0.5, 10 mg/ml injectable	Dog: Antitussive: 0.5–1 mg/kg bid to qid PO 0.05–0.1 mg/kg bid-qid SC Analgesic: 0.2–0.8 mg/kg IV, IM, SQ tid-qid Cat: Analgesic: 0.4 mg/kg tid-qid SC 0.2 mg/kg tid-qid IV 0.5–1.1 mg/kg bid-qid PO	Antitussive, analgesic	Coughing, particularly with large airway disease	Lethargy, anorexia, depression, vomiting	Different injectable concentrations are available—avoid inadvertent overdosing.
Captopril	Capoten 1, 2.5, 25, 50, 100 mg tablets	Dog, Cat: 0.5–2 mg/kg tid PO	Angiotensin-converting enzyme inhibitor, vasodilator	Congestive heart failure, arterial hypertension	Hypotension, anorexia, vomiting, azotemia	
Carnitine (L-Carnitine)	Carnitor 330 mg tablet Generic bulk powder	Dog: 50–100 mg/kg tid PO	Amino acid	Systolic failure due to myocardial carnitine deficiency	Diarrhea (rare)	Use only L-carnitine (avoid D-carnitine or D-L-carnitine, which inactivates carnitine-containing enzyme systems).
Chlorothiazide	Diuril 250, 500 mg tablets 50 mg/ml oral suspension	Dog, Cat: 20–40 mg/kg bid PO (monotherapy)	Thiazide diuretic	Pulmonary edema, ascites, peripheral edema (usually added to furosemide for refractory CHF), arterial hypertension	Hypovolemia, hypokalemia, vomiting, anorexia, azotemia, acid-base alterations	Decrease initial dose 50% when used as adjunctive therapy with furosemide. Decreased glomerular filtration rate (renal failure) reduces thiazide activity.

Table continued on following page

Drug	Trade Names, Formulations*	Approximate Dosage†	Category	Major Indications	Major Side Effects	Comments
Digitoxin	Crystodigin 0.05, 0.1 mg tablets	Dog: 0.02–0.03 mg/kg tid PO	Positive inotrope	Heart failure		
Digoxin	Cardoxin, Lanoxin 0.125, 0.25, 0.5 mg tablets 0.05, 0.1, 0.2 mg capsules 0.05, 0.15 mg/ml oral suspension 0.25 mg/ml injectable	Dog: 0.22 mg/m^2 bid or 0.005–0.01 mg/kg bid PO 0.0025 mg/kg IV bolus, repeat hourly three or four times (total up to 0.01 mg/kg) Cat: 1/4 of 0.125 mg tablet (0.31 mg) eod-sid PO	Positive inotrope, vagomimetic	Heart failure, supraventricular arrhythmias	Arrhythmias, AV block, anorexia, vomiting, diarrhea Toxicity exacerbated by hypokalemia, hyponatremia, hypercalcemia, hypothyroidism, renal failure (digoxin is excreted by the kidney)	Dose based upon lean body weight. Monitor serum levels by sampling blood 8 hours after administration (1–2.4 ng/ml, therapeutic serum concentration). Many adverse drug interactions. Usual maximum dose in Dobermans is 0.25 mg bid.
Diltiazem	Cardizem 30, 60, 90, 120 mg tablets 25 mg/5 ml injectable Cardizem CD 120, 180, 300 mg capsules Dilacor XR 120, 180, 240 mg capsules	*Cardizem* Dog: 0.5–2 mg/kg tid PO Cat: 7.5 mg bid-tid PO Dog, Cat: 0.1–0.2 mg/kg IV bolus, then 2–6 μg/kg/min IV CRI *Cardizem CD* Cat: 10 mg/kg sid PO *Dilacor XR* Dog: 1.5–6 mg/kg sid PO Cat: 30–60 mg sid-bid PO	Calcium channel blocker (benzothiazine)	Supraventricular tachycardia, diastolic dysfunction (e.g., HCM)	Bradycardia, AV block, depression, anorexia, lethargy	May be cautiously combined with β-adrenergic blockers and/or digoxin to treat supraventricular tachycardias. The 60 mg tablets contained within Dilacor XR capsules are used individually for dosing, especially in cats.
Disopyramide phosphate	Norpace 100, 150 mg capsules	Dog: 10–20 mg/kg qid PO	Antiarrhythmic (class 1a)	Supraventricular and ventricular arrhythmias	Proarrhythmic, AV block, hypotension, negative inotropic effect (potentially deleterious with CHF and myocardial failure)	Uncommonly used because the half-life in dogs is only 2 to 3 hours (recommended dosing intervals vary widely)
Dithiazanine iodide	Dizan 10, 50, 100, 200 mg tablets	Dog: 6.6–11 mg/kg PO for 7–10 days	Microfilaricidal	Microfilaria	Vomiting, diarrhea	Uncommonly used today because of effectiveness of ivermectin.
Dobutamine	Dobutrex 12.5 mg/ml, 20 ml vial injectable	Dog: 5–20 μg/kg/min IV CRI Cat: 2–10 (usually, 2–5) μg/kg/min IV CRI	Catecholamine-like agent (adrenergic agonist, positive inotrope)	Acute management of myocardial failure	Arrhythmias at high doses, seizures (cats), arrhythmias	Do not mix with alkalinizing solutions. Dilute 250 mg in 1 liter of 5% dextrose.

Dopamine	Intropin, Dopastat 40 mg/ml, 80 mg/ml, 160 mg/ml, 5 ml vials injectable	*Dopaminergic activity:* Dog, Cat: 1–3 μg/kg/min IV CRI *Inotropic (β_1-adrenergic agonist) activity:* Dog, Cat; 3–5 μg/kg/min IV CRI *Vasopressor (α-agonist) activity:* Dog, Cat: 5–10 μg/kg/min IV CRI	Catecholamine-like agent with dose-dependent dopaminergic/ inotropic/pressor actions	Acute management of CHF or myocardial failure (low doses); vasopressor to treat hypotension/shock (high doses cause peripheral vasoconstriction)	Arterial hypertension, arrhythmias, vomiting	Can counteract effects of β-adrenergic blockers. Protect solution from light. After dilution, must use within 24 h.
Doxapram hydrochloride	Dopram 20 mg/ml injectable	Dog, Cat: 1–10mg/kg IV Neonate: 1–5 mg SC, sublingual, or via umbilical vein	Respiratory stimulant (acts on carotid chemoreceptors)	Respiratory arrest	Seizures, hypertension, arrhythmias	
Edrophonium chloride	Tensilon, Enlon, Reversol 10 mg/ml, 1, 10 ml ampules injectable	Dog, Cat: 0.1–0.2 mg/kg IV	Parasympathomimetic, anticholinesterase	Acute management of supraventricular tachycardia	Cholinergic crisis (tremors, vomiting, diarrhea, bronchospasm, pulmonary edema, respiratory arrest, hypotension, bradycardia)	Very short acting. Administer atropine to treat cholinergic crisis.
Enalapril maleate	Enacard 1, 2.5, 5, 10, 20 mg tablets Vasotec 2.5, 5, 10, 20 mg tablets	Dog: 0.5 mg/kg sid-bid PO Cat: 0.25–0.5 mg/kg eod-bid (typical dose is 0.5 mg/kg sid) PO	Angiotensin-converting enzyme inhibitor	Congestive heart failure, arterial hypertension	Hypotension, anorexia, lethargy Azotemia when administered with excessively high diuretic dosage	Avoid excessive diuresis. Monitor renal function.
Epinephrine	Adrenalin chloride 1 mg/ml (1:1000) injectable Generic 0.1 mg/ml (1:10,000) injectable	Dog, Cat: 0.2 mg IV (double for intratracheal administration)	Catecholamine (α- and β-adrenergic activity)	Cardiac arrest; acute, life-threatening bronchospasm ("asthma"); anaphylactic reactions	Tachyarrhythmias, arterial hypertension, vomiting, tremor, excitement	Duration of effect is very short. Be careful to note the concentration when dosing.
Esmolol	Brevibloc 10 mg/ml, 250 mg/ml injectable	Dog, Cat: 50–500 (usually 50–100) μg/kg IV bolus every 5 min (up to 500 μg/kg max) 50–200 μg/kg/min CRI	β-adrenergic blocker (ultrashort-acting)	Supraventricular tachyarrhythmias, ventricular tachycardia, dynamic outflow tract obstructions	Bradycardia, AV block, hypotension, negative inotropic effect	
Flecainide	Tambocor 50, 100, 150 mg tablets	Dog: 1–5 mg/kg bid-tid PO	Antiarrhythmic (class 1c)	Supraventricular arrhythmias	Proarrhythmic, hypotension, sinus bradycardia, QT interval prolongation, negative inotropic effect, vomiting, anorexia, depression	Selected cases of supraventricular arrhythmias may benefit (e.g., intermittent atrial flutter or atrial fibrillation).

Table continued on following page

Drug	Trade Names, Formulations*	Approximate Dosage†	Category	Major Indications	Major Side Effects	Comments
Furosemide	Lasix Veterinary—12.5, 50 mg tablets Human—20, 40, 80 mg tablets 10 mg/ml syrup Lasix 50 mg/ml injectable	Dog: 2–8 (usually 2–4) mg/kg sid-tid PO 2–4 mg/kg IV, IM, SC PRN Cat: 1–4 (usually 1–2) mg/kg eod-bid PO 0.5–2 mg/kg IV, IM, SC PRN	Loop diuretic	First-line diuretic for CHF (pulmonary edema, ascites, peripheral edema)	Hypochloremic metabolic alkalosis, hypokalemia, hyponatremia, dehydration, hypotension, azotemia	In severe, acute pulmonary edema, IV doses may need to be repeated hourly to effect (max, 8 mg/kg [dog] or 4 mg/kg [cat]).
Glycopyrrolate	Robinul 1, 2 mg tablets 0.2 mg/ml, 20 ml vial injectable	Dog, Cat: 0.005–0.01 mg/kg IV, IM; 0.01–0.02 mg/kg bid-tid SC	Antimuscarinic, parasympatholytic	Sinus bradycardia, 2nd degree AV block	Sinus tachycardia, dry mucous membranes	Oral dose is not established.
Heparin calcium, heparin sodium	Calciparine, Liquaemin Sodium 1000 U/ml, 10,000 U/ml, other concentrations injectable	Dog, Cat: load with 100–200 U/kg IV Dog: 100–500 U/kg tid SC Cat: 100–300 U/kg tid SC	Anticoagulant (primarily to prevent thrombosis)	Thromboembolism	Bleeding	Many protocols and dosing schemes are proposed. Monitor and maintain PTT or ACT at 2–2.5 times pretreatment baseline values.
Hydralazine hydrochloride	Apresoline 10, 25, 50, 100 mg tablets 20 mg/ml, 1 ml vial injectable	Dog: 0.5–3 mg/kg bid PO Cat: 2.5 mg sid-bid PO	Arterial vasodilator (afterload reducer)	CHF, particularly due to severe mitral regurgitation (endocardiosis); systemic hypertension	Hypotension, tachycardia, vomiting	IV dose is not established.
Hydrochlorothiazide	HydroDIURIL, Oretic, Esidrix 24, 50, 100 mg tablets Hydrozide injectable 25 mg/ml injectable	Dog, Cat: 2–4 mg/kg bid PO (monotherapy)	Thiazide diuretic	Pulmonary edema, ascites, peripheral edema (usually added to furosemide for refractory CHF); systemic hypertension	Dehydration, lethargy, electrolyte depletion, acid-base alterations	Decrease initial dose 50% when used as adjunctive therapy with furosemide. Decreased glomerular filtration rate (renal failure) reduces thiazide activity.
Hydrocodone	Hycodan, Tussigon 1.5, 5 mg tablets 1 mg/ml oral suspension	Dog: 0.1–0.25 mg/kg bid qid PO	Antitussive, opiate agonist	Coughing	CNS depression, repiratory depression, sedation	
Isoproterenol	Isuprel 0.2 mg/ml (1:5000) injectable	Dog, Cat: 0.01–2 μg/kg/min IV CRI	Sympathomimetic, β_1- and β_2-adrenergic agonist, positive inotrope, positive chronotrope	Bradycardia, poor cardiac output	Tachyarrhythmias, hypotension with higher doses	Standard dilution is 1 mg/500 ml of 5% dextrose or lactated Ringer's solution and administered CRI to effect.

Isosorbide dinitrate	Isordil, Isorbid, Sorbitrate 2.5, 5, 10, 20, 30, 40 mg tablets	Dog, Cat: 0.2–1 mg/kg bid PO	Nitrate venodilator (preload reducer)	Congestive heart failure	Hypotension	Tolerance can develop but is lessened by intermittent administration.
Ivermectin	Heartguard Canine: 68, 136, 272 µg tablets Feline: 55, 165 µg tablets Ivomec 10 mg/ml solution	Dog: *Heartworm prophylaxis:* 6 µg/kg every month PO Cat: 24 µg/kg every month PO *Microfilaricide:* Dog: 50 µg/kg PO	Macrolide antibiotic	Heartworm chemoprophylaxis, microfilaricide	Transient, mild lethargy, vomiting; uncommonly, tachypnea, tachycardia, shock (related to rapid first-dose reduction of microfilaria)	Use caution in collie dogs.
Lidocaine hydrochloride	Xylocaine 20 mg/ml injectable	Dog: 2.2–8.8 mg/kg IV over 5 min (administer 2.2 mg/kg boluses slowly) 25–80 µg/kg/min IV CRI 4–6 mg/kg IM q2–4 h Cat: 0.25–1.0 mg/kg IV bolus over 5 min (or 1 mg boluses, up to 4 mg max over 5 min) 10–40 µg/kg/min IV CRI	Antiarrhythmic (class 1b)	Ventricular arrhythmias	Seizures, tremors, CNS and respiratory depression, vomiting	For effective results, serum potassium must be normal.
Lisinopril	Prinivil, Zestril 2.5, 5, 10, 20, 40 mg tablets	Dog: 0.25–1.0 (usually 0.5) mg/kg sid-bid PO Cat: 0.25–0.5 mg/kg sid PO	Angiotensin-converting enzyme inhibitor	Congestive heart failure, arterial hypertension	Hypotension, anorexia, lethargy; azotemia when administered with excessively high diuretic dosage	Avoid excessive diuresis. Monitor renal function.
Melarsomine hydrochloride	Immiticide Sterile powder reconstituted to 25 mg/ml injectable	Dog: Two 2.5 mg/kg doses by deep IM injection 24 h apart; repeat in 4 months (standard therapy)	Organoarsenical	Heartworm adulticide chemotherapy	Transient muscle soreness as injection site	Stage treatments for severe heartworm infection (see manufacturer's instructions).
Methimazole	Tapazole 5, 10 mg tablets	Cats: 5 mg bid-tid PO	Antithyroid hormone synthesis agent	Hyperthyroidism	Transient anorexia; vomiting, lethargy; occasional head/neck excoriation; rarely thrombocytopenia, agranulocytosis	Monitor CBC and platelet count every 2–3 weeks for first 3 months of therapy. Determine serum thyroid concentrations and adjust dose accordingly.
Metoprolol	Lopressor 50, 100 mg tablets 1 mg/ml, 5 ml ampule injectable Toprol XL 50, 100, 200 mg tablets	Dog, Cat: 0.25–1.0 mg/kg bid-tid PO	Selective β_1-adrenergic blocker	Tachyarrhythmias, arterial hypertension	Bradycardia, AV block, lethargy, negative inotropic effect, hypotension	When planning to discontinue taper dosage—do not stop abruptly. Response to β-adrenergic blockade can be variable and depends upon the patient's level of sympathetic tone and underlying disease.

Table continued on following page

Drug	Trade Names, Formulations*	Approximate Dosage†	Category	Major Indications	Major Side Effects	Comments
Mexiletine	Mexitil 150, 200, 250 mg capsules	Dog: 4–8 mg/kg tid PO	Antiarrhythmic (class 1b)	Ventricular arrhythmias	Depression, CNS signs, tremors, vomiting, hypotension	In some cases, most effective when combined with β-adrenergic blocker.
Milbemycin oxime	Interceptor 2.3, 5.75, 15, 23 mg tablets	Dog, Cat: 0.5 mg/kg monthly PO	Macrolide antibiotic	Heartworm chemoprophylaxis and microfilaricide	Mild, transient signs related to rapid, first-dose reduction in microfilaremia (weakness, pale membranes, tachypnea)	Side effects related to microfilaria concentration.
Morphine sulfate	Varied	Dog: 0.1 mg/kg IV q2min to effect (up to 1 mg/kg max)—repeat q6h; 0.5–1.0 mg/kg IM, SC PRN Cat: 0.05–0.1 mg/kg IM, SC	Opiate	Acute cardiogenic pulmonary edema	Respiratory depression/arrest, depression, bronchoconstriction, vomiting, defecation, CNS stimulation/behavior changes, hypothermia	
Nadolol	Corgard 40, 80, 120, 160 mg tablets	Dog, Cat: 0.25–0.5 mg/kg bid PO	Nonselective β-adrenergic blocker	Tachyarrhythmias, systemic hypertension, diastolic dysfunction (e.g., HCM)	Bradycardia, depression, AV block, negative inotropic effect, hypotension	Response to β-adrenergic blockade can be variable and depends upon the patient's level of sympathetic tone and underlying disease. When planning to discontinue, taper dosage—do not stop abruptly.
Nitroglycerin	Nitrol, Nitro-Bid, Nitrostat 2% ointment, 20, 30, 60 g tubes (1 inch = 15 mg)	Dog: 1/4–1 inch cutaneously tid-qid Cat: 1/8–1/4 inch cutaneously tid-qid	Venous vasodilator (preload reducer)	Congestive heart failure	Hypotension	Rub ointment into skin (wear gloves—avoid skin contact); wipe off cream base before applying next dose. Tolerance can be lessened by intermittent administration.
Nitroprusside sodium	Nipride, Nitropress 50 mg vial injectable	Dog, Cat: 0.5–10 μg/kg/min CRI	Arterial and venous vasodilator	Acute, severe cardiogenic pulmonary edema	Profound hypotension, cyanogen or thiocyanate toxicity, delirium	Protect solution from light (once reconstituted, the solution is stable for 24 h). Reconstitute in D5W. Discard if solution turns blue, red, or green. Constant arterial blood pressure monitoring required.
Phenylephrine hydrochloride	Neo-Synephrine 10 mg/ml, 1 ml ampules injectable	Dog: 0.005–0.01 mg/kg IV bolus	α_1-Adrenergic agonist	Supraventricular tachycardia, hypotension	Arterial hypertension, reflex sinus bradycardia	Monitor arterial blood pressure. Effect is short lived.

Phenytoin	Dilantin 30, 100 mg capsules 125 mg/5 ml suspension	Dog: 20–35 mg/kg tid PO 1 mg/kg/min IV (up to 6 mg/kg total)	Antiarrhythmic	Digitalis toxic arrhythmias in the dog		Induces hepatic enzymes, therefore may alter kinetics of other drugs (e.g., lidocaine, quinidine, mexiletine).
Potassium chloride	Various Injectable	Dog, Cat: 10–40 mEq/500 ml fluids, administer IV according to serum potassium concentration and cardiovascular status	Electrolyte	Rapid correction of moderate to severe hypokalemia	Iatrogenic hyperkalemia	Administration rate must not exceed 0.5 mEq KCI/kg/h IV.
Potassium gluconate	Kaon elixir 20 mEq/15 ml Tumil-K 2 mEq/1/4 tsp powder 2 mEq tablet 2 mEq/1/2 tsp gel	Dog, Cat: 2.2 mEq/100 kcal of energy/day PO Cat: 2–6 mEq/day	Oral potassium supplement	Nonemergency hypokalemia, prevention of recurrent hypokalemia	Gastrointestinal irritation	
Prazosin hydrochloride	Minipress 1, 2, 5 mg capsules	Dog: 1 mg/15 kg bid-tid PO	Postsynaptic α_1-adrenergic blocker, arterial and venous vasodilator	Congestive heart failure, arterial hypertension	Hypotension, lethargy, vomiting	Tolerance may develop.
Procainamide hydrochloride	Pronestyl, Procamide 250, 375, 500 mg tablets or capsules Pronestyl SR, Procan SR 250, 500, 750, 1000 mg tablets 100 mg/ml, 10 ml vials, 500 mg/ml, 2 ml vials injectable	Dog: 10–20 mg/kg qid (tid if SR preparation) PO 5–15 mg/kg IV (slow bolus); begin low titrate up to effect 25–50 μg/kg/min IV CRI Cat: 2–5 mg/kg bid-tid PO	Antiarrhythmic (class 1a)	Supraventricular and ventricular arrhythmias	Depression, anorexia, diarrhea, vomiting, proarrhythmic, hypotension, QT prolongation, negative inotropic effect	Sustained release (SR) preparations may have variable absorption, and blood concentrations help guide therapy. To be effective, serum potassium concentration must be normal.
Propafenone	Rhythmol 300 mg tablet	Dog: 3–10 mg/kg tid PO	Antiarrhythmic (class 1c)	Supraventricular and ventricular arrhythmias	Bradycardia, some negative inotropic effect	
Propranolol	Inderal 10, 20, 40, 60, 80, 90 mg tablets 4 mg/ml oral suspension Inderal LA (extended release) 60, 80, 120, 160 mg tablets 1 mg/ml, 1 ml ampules injectable	Dog: 0.2–1.0 mg/kg tid PO 0.01–0.1 mg/kg IV (slow bolus) Cat: 2.5–10 mg per cat bid-tid PO 0.01–0.1 mg/kg IV (slow bolus)	Nonselective β-adrenergic blocker	Tachyarrhythmias, arterial hypertension, diastolic dysfunction (e.g., HCM)	Bradycardia, depression, AV block, negative inotropic effect, hypotension	Response to β-adrenergic blockade can be variable and depends upon the patient's level of sympathetic tone and underlying disease. When planning to discontinue, taper dosage—do not stop abruptly.
Quinidine gluconate	Quinaglute Dura-Tabs, Quin-Release (sustained release) 324 mg tablets Duraquin (sustained release) 330 mg tablets 80 mg/ml, 10 ml vials injectable	Dog: 5–20 mg/kg tid-qid (tid for sustained release) IM, PO 5–10 mg/kg IV (slow bolus) Dose calculated on amount of quinidine base. See comments.	Antiarrhythmic (class 1a)	Supraventricular and ventricular arrhythmias	Hypotension (especially by IV route), proarrhythmic, anorexia, vomiting, diarrhea, prolonged QT interval, negative inotropic effect	Injectable solution is sensitive to light. Be cautious when used with digoxin (elevates serum digoxin concentration). Serum potassium must be normal to be effective. Quinidine gluconate is 62% base (324 mg quinidine gluconate = 202 mg quinidine base).

Table continued on following page

Drug	Trade Names, Formulations*	Approximate Dosage†	Category	Major Indications	Major Side Effects	Comments
Quinidine sulfate	Cin-Quin, Quinora 100, 200, 300 mg tablets; 200, 300 mg capsules 200 mg/ml injectable Quinidex Extentabs (sustained release) 300 mg tablets	Dog: 5–20 mg/kg qid IM, PO for sulfate, tid for sustained release 5–10 mg/kg IV (slow bolus) Dose is calculated on amount of quinidine base. See comments.	Antiarrhythmic (class 1a)	Supraventricular and ventricular arrhythmias	Hypotension (especially by IV route), proarrhythmic, anorexia, vomiting, diarrhea, prolonged QT interval, negative inotropic effect	Injectable solution is sensitive to light. Use caution when used with digoxin (willincrease serum digoxin concentrations). Serum potassium concentration must be normal to be effective. Quinidine sulfate is 83% quinidine base (300 mg quinidine sulfate = 250 mg quinidine base).
Ramipril	Altace 1.25, 2.5, 5, 10 mg capsules	Dog: 0.5 mg/kg sid-bid PO Cat: 0.5 mg/kg sid PO	Angiotensin-converting enzyme inhibitor	Congestive heart failure, arterial hypertension	Hypotension, anorexia, lethargy; azotemia when administrated with excessively high diuretic dosage	Avoid excessive diuresis. Monitor renal function.
Sotalol	Betapace 80, 160, 240 mg tablets	Dog: 0.5–2 mg/kg bid PO Cat: 1/8 of 80 mg tab bid PO	Antiarrhythmic (class II and class III action)	Ventricular arrhythmias	Proarrhythmic, bradycardia, QT prolongation, negative inotropic effect, depression, anorexia	
Spironolactone	Aldactone 25, 50, 100 mg tablets	Dog, Cat: 1–2 mg/kg bid PO (usually combined with furosemide or thiazide diuretic)	Aldosterone competitive antagonist diuretic (potassium-sparing diuretic)	Congestive heart failure, especially when limiting potassium loss is desirable	Hyperkalemia, dehydration, vomiting, anorexia, lethargy, acid-base disturbances	Rarely used as monotherapy. Monitor potassium concentration, especially when given with angiotensin-converting enzyme inhibitors.
Streptokinase	Streptase 30,000 IU/ml injectable 250,000, 750,000, or 1,500,000 IU/6.5 ml vials injectable	Cat: 90,000 IU IV infusion over 1 h, then 45,000 IU/h IV CRI for a total of 6–8 h	Thrombolytic agent	Arterial thromboembolism	Bleeding, hyperkalemia	Causes a generalized lytic state (avoid if animal is heparinized or taking Coumadin). Acute, severe hyperkalemia due to reperfusion of skeletal muscles may follow.
Taurine	Generic	Dog: 500 mg bid PO Cat: 250 mg bid PO	Amino acid	Taurine deficiency myocardial failure		
Terbutaline	Brethine, Bricanyl 2.5, 5 mg tablets 1 mg/ml, 1 ml ampule injectable	Dog: 1.25–5 mg bid PO Cat: 0.15 mg/kg (or approx 0.625 mg/cat) bid PO	Bronchodilator, β_2-adrenergic agonist	Bronchoconstriction	Sinus tachycardia, anxiousness, nervousness, vomiting	

Theophylline	Theo-Dur (sustained release) 100, 200, 300, 450 mg tablets Choledyl (sustained action)	Dog: 20 mg/kg bid PO Cat: 25 mg/kg sid PO Dog: 25–30 mg/kg bid PO	Bronchodilator, competitive phosphodiesterase inhibitor	Bronchodilation	Tachycardia, anxiousness, depression, vomiting, diarrhea, anorexia, tachypnea	
Thiacetarsamide sodium	Carparsolate 10 mg/ml injectable	Dog: 2.2 mg/kg bid IV for 2 days	Organoarsenical	Heartworm adulticide chemotherapy	Hepatotoxic; may cause severe inflammation and necrosis at injection site if injected subcutaneously	Does not dependably kill all adult worms.
Tissue plasminogen activator (t-PA)	Activase 1 mg/ml, 50, 100 mg vial injectable	Cat: 0.25–1 mg/kg/h (for a total dose of 1–10 mg/kg) IV	Fibrinolytic agent (tissue plasminogen activator)	Thrombolytic therapy	Bleeding, hyperkalemia, metabolic acidosis	Avoid if animal is heparinized or taking Coumadin. Acute, severe hyperkalemia due to reperfusion of skeletal muscles may follow.
Tocainide	Tonocard 400, 600 mg tablets	Dog: 10–20 mg/kg bid PO	Antiarrhythmic (class 1b)	Ventricular arrhythmias	Anorexia, CNS toxicity (tremors, ataxia), corneal edema	Side effects are common.
Triamterene	Dyrenium 100 mg capsules	Dog, Cat: 1–2 mg/kg bid PO	Potassium-sparing diuretic	Congestive heart failure, especially when limiting potassium loss is desirable	Hyperkalemia, dehydration, vomiting, anorexia, lethargy, acid-base disturbances	Rarely used as monotherapy. Monitor potassium concentration, especially when given with angiotensin-converting enzyme inhibitors.
Verapamil	Calan, Isoptin 80, 120 mg tablets (240 mg sustained release tablet) 5 mg/ml, 2, 4, 5 ml vials injectable	Dog: 1–5 mg/kg tid PO 0.05 mg/kg IV (slow bolus) q10–30 min (up to 0.15 mg/kg max)	Calcium channel blocker	Supraventricular tachycardia	Hypotension, bradycardia, AV block, negative inotropic effects, anorexia	Use cautiously if combined with β-adrenergic blockers
Warfarin	Coumadin 1, 2, 2.5, 4 mg tablets	Dog: 0.1–0.2 mg/kg sid PO Cat: 0.25–0.5 mg/cat sid PO	Anticoagulant	Prevent thromboembolism	Bleeding	Protect from light. Adjust dosage to maintain the prothrombin time to twice normal; or, adjust INR to maintain a value of 2.0–3.0 as follows: INR = [Cat or Dog Prothrombin Time + Control Prothrombin Time]^{ISI}

Constant Rate Infusion (CRI) Dosing Formula Worksheet

Volume (ml) of fluid to be removed from *and* Volume (ml) of drug to be added back to the fluid bottle or bag =

$$\frac{\left[\frac{\text{CRI dose } (\mu g/kg/min)}{1000\ \mu g/mg}\right] \times \text{Body weight (kg)} \times \text{Volume of fluids (ml) to be administered} \times 60\ \text{min/h}}{\text{Drip rate of fluids (ml/hr) to be given‡} \times \text{Concentration of drug (mg/ml)}}$$

‡For routine maintenance, the volume of fluid to be administered approximates 2.5 ml/kg/h (adjust according to patient hydration, urine output, etc.).

INDEX

Note: Page numbers in *italics* refer to illustrations; page numbers followed by (t) refer to tables.

Abdomen, compression of, in basic life support, 434
  cranial, radiographic appearance of, 127
  examination of, 50
  swollen, significance of, 44, 47
  ultrasonography of, signs of heart failure on, 153
    in dog, *153*
ACE inhibitors. See *Angiotensin-converting enzyme inhibitors.*
Acepromazine, for anxiety, in cat with pulmonary edema, 260, 260(t)
Acoustic enhancement, 132
Acoustic impedance, 131
Acoustic shadowing, 132
Acquired atrioventricular valve disease, chronic. See *Endocardiosis.*
Acquired heart disease, 536–559, 828–839. See also *Endocardiosis.*
  arrhythmias associated with, in cat, 387–388
  prevalence of, in cat, 465
    in dog, 463–465
Acquired pericardial disease, 685–696. See also *Cardiac tamponade; Pericardial effusion.*
Acquired valvular disease, 536–559. See also *Endocardiosis.*
Acromegaly (hypersomatotropism), 766
  in cat, 656
    cardiovascular abnormalities associated with, 656
Action potentials, 70–71, *71, 292*
  heart damage affecting, 293–295, *294, 295*
Addison's disease (hypoadrenocorticism), 763–764
Adenosine, adverse effects of, 315(t), 908(t)
  for arrhythmias, 908(t)
    in dog, 315(t)
      factors limiting use of, 349
    in man, 349
  recommended dosages of, for dog, 908(t)
Adrenal gland, dysfunction of, 763–765
Adulticide therapy, for heartworm disease, in cat, 733
  in dog, 710–713
    ancillary drugs used in, 713–714
    thromboembolism due to, 719
Advanced life support, 435–437, *436.* See also *Cardiopulmonary cerebral resuscitation.*
Afghan hound. See also *Dog(s).*
  cardiomegaly in, dilated cardiomyopathy and, *256*
  dilated cardiomyopathy in, *583*
    radiographic findings associated with, *256*
  heart failure in, dilated cardiomyopathy and, *256*
    radiographic findings associated with, *256*
  M-mode echocardiography in, normal findings on, 145(t)
  pulmonary edema in, dilated cardiomyopathy and, *256*
    heart failure and, *256*
Afterdepolarizations, delayed, 298–299, *300*
  early, 298, *299*
Afterload, 25
Age, and changes in blood pressure, in dog, 796(t)
  and changes in cardiovascular responsiveness, 839
  and risk of infectious endocarditis, in dog, *568*
  and risk of pericardial/peritoneopericardial diaphragmatic hernia, in cat, *683*
    in dog, *683*
Air bronchograms, as sign of pulmonary edema, *256, 257, 258, 259, 261*
Airway, in basic life support, 429, 431
Albumin, in management of shock, 279
Albuterol, adverse effects of, 908(t)
  bronchodilation with, 908(t)
  recommended dosages of, for cat, 908(t)
    for dog, 908(t)
Aldosterone, 765
Aldosteronism (Conn's disease), 765
  electrocardiographic findings in, 765, *765*
Aliasing, and Doppler-derived blood flow velocity, *137,* 139–140
Alpha-adrenergic blocking agents. See also *Prazosin.*
  for hypertension, 805(t), 807
Alveolar-capillary structure, of lung, 251, *252*
  effects of injury to, 253–254. See also *Pulmonary edema.*
Ambulatory electrocardiography, 102, *102.* See also *Electrocardiography.*
  in detection of arrhythmias and syncope, 448, *449*
Ambulatory electrocardiography *(Continued)*
  in detection of canine arrhythmias, 331–332. See also *Dog(s), electrocardiography in.*
American Cocker spaniel. See also *Dog(s).*
  dilated cardiomyopathy in, *583*
    cardiomegaly accompanying, *591*
    radiographic findings associated with, *591*
Amikacin, for endocarditis, 577(t)
Aminophylline. See also *Theophylline.*
  adverse effects of, 908(t)
  as bronchodilator, 908(t)
  for pulmonary edema, 260(t)
  for sick sinus syndrome, in dog, 450
  for tussive syncope, in dog, 453
  recommended dosages of, for cat, 908(t)
    for dog, 904(t), 908(t)
Amiodarone, 322–323
  adverse effects of, 315(t), 323, 908(t)
    on dog, 367
  drugs interacting with, effects of, 326(t)
  electrocardiographic parameters affected by, 311(t), 323
  for arrhythmias, 322, 908(t)
    in dog, 315(t), 350, 354, 363, 366
  for atrial fibrillation, in dog, 354
  for supraventricular tachycardia, in dog, 350
  for ventricular tachycardia, in dog, 363, 366
  recommended dosages of, for dog, 904(t)
Amlodipine, adverse effects of, 908(t)
  for heart failure, 237(t), 238
    in dog with mitral regurgitation, 552
  for hypertension, 805(t), 908(t)
  for mitral regurgitation and heart failure, in dog, 552
  recommended dosages of, for cat, 908(t)
    for dog, 908(t)
Amoxicillin, for endocarditis, 577(t)
Ampicillin, for endocarditis, 577(t)
Amputation, of paralyzed limb, in cat with thromboembolism, 665, *666*
Amrinone, adverse effects of, 908(t)
  for heart failure, 224, 229(t), 234, 908(t)
  recommended dosages of, for dog, 904(t), 908(t)
Amyloidosis, cardiac manifestations of, 776
Analgesics, for cat, 854(t)
  for dog, 854(t)
Anechoic tissue, 132. See also *Echocardiography.*

Anemia, 789–790
cardiac manifestations of, 772, 789, 790
Anesthesia, 853–864
agents used in, 854(t), 858(t), 861–862
drug interactions with, 856
bradycardia induced by, 867
in cat, *92*
for cardiac catheterization, 174
monitoring response to, 863–864
premedicants used in, 858(t), 858–861, 859(t)
risks of, 857, 857(t), 858
Angiocardiography, 187–190
aortic stenosis on, in dog, *189*
ASD-related findings on, 498–499
complications associated with, 180
congenital heart defects on, 475
DCM-related changes on, in cat, 649, *649*
double-chambered right ventricle on, in dog, *481*
HCM-related changes on, in cat, 630, *633*, *662*
mitral valve dysplasia on, 524
in dog, *189*, *525*
normal findings on, in cat, *188*
in dog, *188*
PDA-related findings on, 508–509
in cat, *189*
in dog, *508*
pulmonic regurgitation on, 559
pulmonic stenosis on, 481–482
in dog, *189*, *484*
radionuclide, 194, *194*
in evaluation of shunts, *194*, 194–195, *195*, *196*
in evaluation of ventricular function, 195–199, *197*, 197(t), *198*
RCM-related changes on, in cat, 644, *644*
subaortic stenosis on, in dog, *189*
tetralogy of Fallot on, 517
in cat, *514*
in dog, *189*, *514*
tricuspid valve dysplasia on, 525
VSD-related findings on, 505
in dog, *189*, *501*, *502*
Angiography. See also *Angiocardiography.*
aortic, distal embolus on, in cat, *660*, *662*
Angiotensin-converting enzyme inhibitors, 240
for DCM and heart failure, in cat, 651
in dog, 597
for HCM, in cat, 635, 636, 640
for HCM and myocardial infarction, in cat, 635
for heart failure, 237(t), 240–242
adverse effects of, 242–243
in cat with dilated cardiomyopathy, 651
in dog with dilated cardiomyopathy, 597
in dog with mitral regurgitation, 551
International Small Animal Cardiac Health Council recommendations regarding, 905(t)
for hypertension, 805(t), 807–808
for mitral regurgitation and heart failure, in dog, 551
for myocardial infarction, in cat with hypertrophic cardiomyopathy, 635
recommended dosages of, for cat, 903(t)
for dog, 903(t)
Angiotensin II, effects of, *211*, 211–212
Anthracyclines, as cardiotoxins, 609
Antiarrhythmic(s), 307–327, 348–355, 362–368. See also specific agents, e.g., *Lidocaine.*
adverse effects of, 315(t)
Antiarrhythmic(s) *(Continued)*
classification of, 307–310, 309(t), 310(t)
drugs interacting with, effects of, 326(t)
electrophysiologic and cardiographic parameters affected by, 309(t), 310(t), 311(t)
in dog, 361, *361*
in dog with atrial flutter or fibrillation, *353*
in dog with supraventricular tachycardia, *349*, *350*, *351*
emergency use of, 437–438
parasympathetic effects of, 309(t)
pharmacokinetics of, 310, 312–313
recommended dosages of, for cat, 315(t)
for dog, 315(t), 348–354, 904(t)
sympathetic effects of, 309(t)
Antibiotic(s), for endocarditis, 576, 577(t)
for shock, 284(t), 284–285
Antibiotic prophylaxis, against endocarditis, 577–578
against heartworm disease, in cat, 734
in dog, 721
Anticholinergics, as preanesthetic agents, 858(t), 858–859, 859(t)
Anticoagulant therapy, for thromboembolism, in cat, 664–665
complications associated with, 665, *665*
Antihypertensives, 805(t), 806–808
Antiplatelet therapy, for thromboembolism, in cat, 665
Antiprostaglandins, in management of shock, 285–286
Antithyroid drugs, for hyperthyroidism, in cat, 786–787, 913(t)
Anxiolytics, for cat with pulmonary edema, 260, 260(t)
for dog with pulmonary edema, 260, 260(t)
Aorta, 21
coarctation of, 494
descending, compression or cross-clamping of, in basic life support, 435
distal, as site of "saddle" embolism. See *Embolism, distal aortic.*
thromboembolism of, prevalence of, in cat, 467
Aortic arch(es), 21
development of, 6–7, *7*
enlarged radiographic appearance of, 119–120
right, persistent, 528
in cat, *528*
in dog, breed predisposition to, 462
prevalence of, 459(t), 462
surgery for, 878
Aortic insufficiency. See *Aortic regurgitation.*
Aorticopulmonary septal defect, 528
pathology of, 826
Aortic regurgitation, 559
aortic stenosis and, 492
echocardiographic findings associated with, 492
in dog, *490*
heart failure associated with, treatment of, 228
heart murmur accompanying, in dog, 61
Aortic stenosis, 158–159, 485–494
angiocardiographic findings associated with, in dog, *189*
aortic regurgitation accompanying, 492
echocardiographic findings associated with, 492
in dog, *490*
canine breed predisposition to, 460, 460(t)
Aortic stenosis *(Continued)*
echocardiographic evidence of, 159, 488, *489*, 490
in dog, *136*, 159, *159*, *490*, *491*, *492*
electrocardiographic findings associated with, 490
in dog, *489*
gross morphology of, in cat, 823
in dog, 486–487, *488*, 822–823
heart failure associated with, treatment of, 228
heart murmur accompanying, in dog, *60*, 60–61
myocardial compensation for, 207(t)
myocardial fibrosis associated with, 487–488
echocardiographic evidence of, 488, *489*
prevalence of, in dog, 459(t), 460
radiographic findings associated with, 489
in dog, *491*
surgery for, 872–873
Aortic valve, 20
blood flow in or across, Doppler-derived velocity of, in cat, 154(t)
in dog, 154(t)
regurgitant. See *Aortic regurgitation.*
stenosis of. See *Aortic stenosis.*
surgical dilation of, 873
Apex beat, 50
Apoptosis, 818(t)
myocardial, heart failure and, 818–819
Arrhythmia(s), 331–375, 386–398
abnormal impulse conduction and, 299–303
acquired heart disease and, in cat, 387–388
automaticity and, 296–297, *297*, *298*
canine breed predisposition to, 465–466
cardiomyopathies and, in cat, 387, 387(t)
in dog, 369
causes of, 295–303, 296(t), 308(t)
conduction blocks and, 299–300. See also *Atrioventricular block.*
congenital heart disease and, in cat, 386–387
consequences of, in cat, 388
diagnosis of, in cat, 388–389
in dog, 331–332
dilated cardiomyopathy and, in cat, 387(t)
treatment of, 650
in dog, 369–370, 590, 590(t), 591
treatment of, 597, 598, 895–896
evidence of drug effectiveness in, on ECG, *353*
drugs for. See *Antiarrhythmic(s).*
electrocardiographic detection of, 77(t), 90–100
in cat, 389–390
results of. See specific findings cited under *Cat(s), electrocardiography in.*
in dog, 331–332
results of. See specific findings cited under *Dog(s), electrocardiography in.*
electrocardiographic detection of syncope accompanying, 448–449, *449*
electrophysiologic mechanisms for, 295–303, 296(t)
enhanced impulse initiation in ectopic foci and, *296*, 296–299
frequency of, by type, in dog, 458(t), 465–466

Arrhythmia(s) *(Continued)*
heart failure and, in cat with cardiomyopathy, 387, 387(t)
in dog, 224, 371
treatment of, 224–225
heart sound variations in relation to, 57–58
Holter monitoring for. See also *Electrocardiography.*
in dog, 331–332
Holter monitoring for syncope accompanying, 448, *449*
hyperthyroidism and, 783(t), 786
hypertrophic cardiomyopathy and, in cat, *387,* 387(t), 626, 630, 631(t), 635–636
in cat, 386–398
in dog, 331–375
infectious endocarditis and, 573, 575, 576
junctional, 97
in dog, *97,* 346–347
management of. See *Antiarrhythmic(s); Pacemaker.*
modulating factors in, 347
myocardial diseases and, in cat, 387, 387(t)
in dog, 369
pacemaker for. See *Pacemaker.*
pacemaker-induced, 423
re-entrant activation and, 102, 300–303, *301.* See also *Re-entrant tachycardia.*
restrictive cardiomyopathy and, in cat, 387(t)
right ventricular dysplasia and. See *Arrhythmogenic right ventricular dysplasia.*
sinus, 92, *92*
substrate for, 347
supraventricular, in cat, 391–393
in dog, 338–347
differentiation of, from ventricular arrhythmias, 332(t), 332–338
P wave and QRS complex in, 333–334, *336, 337, 338*
QRS complex morphology in, 333, *333, 334, 335*
unreliability of rhythm (ir)regularities and pause length in, 334–335
vagal maneuvers in, 335–336, 338, *339, 340*
treatment of, 347–355
adverse effects of, 351–352
evidence of drug effectiveness in, on ECG, *349, 350, 351, 353*
syncope associated with, 450–451
electrocardiographic monitoring for, 448–449, *449*
treatment of, 450, 451
triggers for, 297–298, 347
ventricular, in cat, 98, 99, 396–398, *397*
in dog, 98, 99, *99,* 355–361
lethality of, 356–357, 370, 836
vs. supraventricular arrhythmias. See *Arrhythmia(s), supraventricular, in dog, differentiation of.*
mechanisms for, electrophysiologic, 296(t)
Arrhythmogenic right ventricular dysplasia, in cat, 653–655, *654, 655,* 831–832
in dog, 609
in man, 608–609
Arterial blood pressure. See *Blood pressure; Hypertension.*
Arterial catheterization, peripheral, in CPCR, 441
in left-sided cardiac catheterization, 177, *178,* 179–180. See also *Cardiac catheterization.*
Arterial pulse(s), 62–64, *63*
abnormal, in infectious endocarditis, 573
monitoring of, in CPCR, 440
Arterial thromboembolism, in cat, 658–667. See also *Thromboembolism.*
Arteriopathy, pulmonary, plexogenic, Eisenmenger's physiology and, 826
Arteriotomy, pulmonary, inflow occlusion and, for pulmonic stenosis, 870–871, *871*
Arteriovenous fistulas, 790–791
cardiac manifestations of, 762, 790
diagnosis of, 790
echocardiography in, 790, *791*
Arthritis, infectious endocarditis and, 570
Ascites, in surgical patient, 857
significance of, 47
ASD. See *Atrial septal defect.*
Ashman phenomenon, 100, 101
Aspirin, adverse effects of, 908(t)
for myalgia, in cat with ischemic limb, 666
for thromboembolism, 908(t)
in cat, 665, 908(t)
in dog, 908(t)
recommended dosages of, for cat, 904(t), 908(t)
for dog, 904(t), 908(t)
for dog with heartworm disease, 713, 714
Asystole, ventricular, 99–100
Atenolol, 321–322
adverse effects of, 315(t), 322, 908(t)
electrocardiographic parameters affected by, 311(t)
for arrhythmias, 321, 908(t)
in cat, 315(t), 398
in cat with hypertrophic cardiomyopathy, 636
in dog, 315(t), 349
in dog with dilated cardiomyopathy, 598
for congenital heart disease, 485(t)
for DCM and arrhythmias, in dog, 598
for HCM and arrhythmias, in cat, 636
for HCM and left ventricular outflow tract obstruction, in cat, 639
in dog, 606
for HCM and myocardial infarction, in cat, 635
for heart failure, 243
in cat with hypertrophic cardiomyopathy, 637
for hypertension, 805(t), 908(t)
for hyperthyroidism, 786, 787
for left ventricular outflow tract obstruction, in cat with hypertrophic cardiomyopathy, 639
in dog with hypertrophic cardiomyopathy, 606
for myocardial infarction, in cat with hypertrophic cardiomyopathy, 635
for supraventricular tachycardia, in dog, 349
for ventricular tachycardia, in cat, 398
recommended dosages of, for cat, 903(t), 908(t)
for dog, 908(t)
Atrial extrasystoles, 94
in cat, 391, *391*
in dog, *94*
Atrial fibrillation, 94–95
in cat, 392, *392*
in dog, *95,* 343, *343, 344,* 345, *401*
and dilated cardiomyopathy, 588, 591
lethality of, *601*
Atrial fibrillation *(Continued)*
occurring asymptomatically, among large breeds, 466
temporary, 354
treatment of, 352, 354
evidence of drug effectiveness in, on ECG, *353*
murmurs and altered heart sounds associated with, 57
Atrial flutter, 94–95
in cat, 391–392
in dog, *95, 342,* 342–343, *401*
treatment of, 352
evidence of drug effectiveness in, on ECG, *353*
Atrial septal defect, 157–158, 495–499
angiocardiographic findings associated with, 498–499
canine breed predisposition to, 462
corrected, echocardiographic findings following, in dog, Plate 9
echocardiographic evidence of, 157–158, 498
in dog, *134, 135, 496,* Plates 7 & 8
electrocardiographic findings associated with, 498
in dog, *499*
gross morphology/pathology of, 495–496, 825
in cat, *495*
heart murmur accompanying, 61
ostium primum–type, 495, 825
echocardiographic findings associated with, in dog, *496,* Plate 8
gross morphology of, 825
in cat, *495*
ostium secundum–type, 157, 495, 825
echocardiographic findings associated with, in dog, *134*
gross morphology of, 825
in cat, *495*
prevalence of, in dog, 459(t), 462
shunt(ing) accompanying, 157, 496–497
echocardiographic findings associated with, in dog, *134, 135*
sinus venosus–type, 157, 495, 825
echocardiographic findings associated with, in dog, *135*
surgery for, 873
echocardiographic findings following, in dog, Plate 9
Atrial standstill, persistent. See *Atrioventricular myopathy (persistent atrial standstill).*
Atrial tachycardia, 96
in cat, 391, *392*
in dog, ectopic, *341,* 341–342
treatment of, 350–351
Atrioventricular annulus, measurement of, 846–847
Atrioventricular block, 81–84
in cat, 82, *83,* 394–396, *395, 401*
as indication for pacemaker, 403
in dog, 82, *82, 83,* 375, *401*
as indication for pacemaker, 402
pharmacotherapy for, 909(t)
with altered heart sounds, 57–58
Atrioventricular junctional arrhythmias, 97, *97*
Atrioventricular myopathy (persistent atrial standstill), 81, 836–837
in cat, 392, 658, 836
electrocardiographic characteristics of, 81, *81*
in dog, 403, 466, 607–608, *608,* 836, *837*
electrocardiographic characteristics of, 81

Atrioventricular myopathy (persistent atrial standstill) *(Continued)*
hyperkalemia and, *89*
Atrioventricular nodal re-entrant tachycardia, in dog, 345–346, *346*
Atrioventricular node, 22
Atrioventricular node–dependent supraventricular tachycardia, in dog, 338, 345–347
treatment of, 354–355
Atrioventricular node–independent supraventricular tachycardia, in dog, 338–345
treatment of, 348–354
Atrioventricular orifice, left, 17
right, 17
Atrioventricular septal defects, pathology of, 825
Atrioventricular valve(s), 20. See also *Mitral valve* and *Tricuspid valve.*
Atrioventricular valve disease, chronic acquired. See *Endocardiosis.*
Atrioventricular valve dysplasia, 158
echocardiographic findings associated with, 158
in dog, *158*
pathology of, 824
Atrium (atria), 16–17. See also *Atrial* entries.
contraction sequence for, in cardiac pacing, 411, 412
left, 15, 17
blood stasis in, and risk of thrombosis, in cat, 659
and spontaneous echocardiographic contrast ("smoke"), 167
enlargement of. See also *Cardiomegaly.*
electrocardiographic findings associated with, 78, *78*
radiographic appearance of, 113–116
opening of, at necropsy, 846
rupture of, endocardiosis and, 554–555, *555*
right, 15, 16–17
enlargement of. See also *Cardiomegaly.*
electrocardiographic findings associated with, 77–78, *78*
radiographic appearance of, 116
hemangiosarcoma of, 880
echocardiographic findings associated with, *166*, 168, *694*
in dog, *166*, *687*, *694*, 880
surgery for, 880
opening of, at necropsy, 846
septum between, 17
defect in. See *Atrial septal defect.*
formation of, 5, *6*
silent. See *Atrioventricular myopathy (persistent atrial standstill).*
Atropine, adverse effects of, 315(t), 909(t)
as preanesthetic agent, 858(t), 859(t)
emergency use of, 431(t), 438
for arrhythmias, in dog, 315(t)
for atrioventricular block, 909(t)
in cat, 396
for bradycardia, 909(t)
for cardiopulmonary arrest, 431(t), 438
for cardiovascular drug–induced hypotension, in dog, 351
recommended dosages of, for cat, 904(t), 909(t)
for dog, 904(t), 909(t)
Attenuation, in ultrasonography, 131
Auscultation, 50–53, *51*, *53*. See also *Heart murmurs; Heart sound(s).*
Automaticity, and arrhythmias, 296–297, *297*, *298*
Automatic junctional tachycardia (ectopic junctional tachycardia), in dog, 346–347
Axial resolution, in ultrasonography, 131
Azimuthal resolution (elevational resolution), in ultrasonography, 131

Bacteremia, and endocarditis, 568. See also *Endocarditis, infectious.*
and shock. See *Sepsis* and *Septic* entries.
Bacterial endocarditis. See *Endocarditis, infectious.*
Bacterial myocarditis, 833
in cat, *833*
in dog, 612
Balloon valvuloplasty, for pulmonic stenosis, 190, 868
Banding, of pulmonary artery, in surgery for ventricular septal defects, 874, *874*
Basic life support, 429, 431–435, *432*. See also *Cardiopulmonary cerebral resuscitation.*
Basset hound. See also *Dog(s).*
electrocardiography in, signs of pulmonic stenosis and right ventricular hypertrophy on, *482*
Beagle crossbreed. See also *Dog(s).*
echocardiography in, heartworm-related changes on, *711*
Benazepril, adverse effects of, 909(t)
for HCM, in cat, 635, 636, 640
for HCM and myocardial infarction, in cat, 635
for heart failure, 237(t), 242, 909(t)
for hypertension, 805(t), 909(t)
for myocardial infarction, in cat with hypertrophic cardiomyopathy, 635
recommended dosages of, for cat, 909(t)
for dog, 909(t)
Benzodiazepines, as preanesthetic agents, 858(t), 859(t), 860
Beta-adrenergic blocking agents. See also specific drugs, e.g., *Propranolol.*
cardioselectivity of, 311(t)
for arrhythmias, 315(t)
in cat, 398
in cat with hypertrophic cardiomyopathy, 636
in dog, 348, 352
in dog with dilated cardiomyopathy, 598
for atrial fibrillation, in dog, 352
for DCM, in cat, 652
in man, 652
for DCM and arrhythmias, in dog, 598
for HCM, 218
in cat, 635, 636, 637, 639
for HCM and arrhythmias, in cat, 636
for HCM and left ventricular outflow tract obstruction, in cat, 639
in dog, 606
for HCM and myocardial infarction, in cat, 635
for heart failure, 243–244
adverse effects of, 244
in cat with hypertrophic cardiomyopathy, 637
International Small Animal Cardiac Health Council recommendations regarding, 905(t)
for hypertension, 805(t), 806–807
for hyperthyroidism, 786, 787
for left ventricular outflow tract obstruction, in cat with hypertrophic cardiomyopathy, 639
Beta-adrenergic blocking agents *(Continued)*
in dog with hypertrophic cardiomyopathy, 606
for myocardial infarction, in cat with hypertrophic cardiomyopathy, 635
for supraventricular tachycardia, in dog, 348
for surgical patient, 856
for ventricular tachycardia, in cat, 398
recommended dosages of, for cat, 903(t)
for dog, 903(t)
Bicarbonate, use of, in CPCR, 431(t), 438
in management of shock, 286
Bidirectional shunt, atrial septal defect and, in dog, echocardiographic findings associated with, *135*
Bioavailability, drug, dosage calculations based on, 310
Bipolar pacemaker, 409, *410*. See also *Pacemaker.*
Bipyridine compounds (PDE III inhibitors), for heart failure, 224, 229(t), 234–235
Blalock anastomosis, in surgery for tetralogy of Fallot, 875, *875*
Bleeding, gastrointestinal, shock and, 286
secondary to warfarin therapy, in cat, 665, *665*
Blood, hypercoagulability of, secondary to shock, 287
viscosity of, 33
increase in, cardiac manifestations of, 772–773
Blood cysts, in tricuspid valve, prevalence of, in dog, 463–464
Blood flow. See also *Circulation.*
coronary, 33–34, *34*
fetal, 8, *8*
transition from, to circulation in newborn animal, 8–9
laminar, 137
monitoring of, in CPCR, 440
regurgitant, quantification of, via Doppler echocardiography, 154
sites of. See *Aortic regurgitation; Mitral regurgitation;* etc.
Reynold's number for, 137
turbulent, 137
velocity of, Doppler-derived. See *Doppler echocardiography, blood flow velocity derived from.*
Blood pressure, 798–800. See also *Hypertension.*
effect of pacemaker on, 411
in dog, *412*
heart rate in relation to, 28, *28*
in cat, 796(t)
elevated, 468
pharmacotherapy for, 805(t)
in dog, 796(t)
breed differences in, 797(t)
changes in, with aging, 796(t)
elevated, 468, 797
pharmacotherapy for, 805(t)
measurement of, 803–804
monitoring of, in anesthetized patient, 863
in CPCR, 440
in management of shock, 280–281
regulation of, 798–800
Blood products, in management of shock, 279–280
Blood sample, as source for culture, in diagnosis of IE, 575. See also *Endocarditis, infectious.*
Blood stasis, in left atrium, and risk of thrombosis, in cat, 659

Blood stasis *(Continued)*
and spontaneous echocardiographic contrast ("smoke"), 167, 636
Body weight, excessive, cardiac manifestations of, 776
loss of, causes of, 44, 47, 744
ratio of heart weight to, 847
in cat, 847(t)
in cat with cardiomyopathy, 847(t)
in dog, 847(t)
Borrelia burgdorferi infection, in dog, 612
and myocarditis, 612
Bowel, embolization to, in infectious endocarditis, *571*
Boxer. See also *Dog(s).*
arrhythmias in, cardiomyopathy and, 369
atrial septal defect in, echocardiographic findings associated with, *134*
cardiomyopathy and arrhythmias in, 369
dilated cardiomyopathy in, *583, 584*
electrocardiographic findings associated with, 590, 590(t)
pacemaker problems in, electrocardiographic evidence of, *424*
vasovagal syncope in, 452
Brachial artery embolization, in cat, sequelae of, *660*
Bradyarrhythmias. See also *Bradycardia.*
in cat, 390, *401*
and syncope, 451
as indication for pacemaker, 400, 403
in dog, 371–375, *401*
and syncope, 451
as indication for pacemaker, 400, 402–403
with altered heart sounds, 57–58
Bradycardia. See also *Bradyarrhythmias.*
anesthesia-induced, 867
in cat, *92*
pharmacotherapy for, 909(t)
sinus, 91
in cat, 390
surgical anesthetic complications and, *92*
Brain, diseases of, cardiac manifestations of, 772
embolization to, in infectious endocarditis, *571*
Breathing, in basic life support, 431–433
observation of, in diagnosis of cardiovascular disease, 46
Breed predisposition. See *Canine breed predisposition; Feline breed predisposition.*
Bretylium, 323
adverse effects of, 315(t), 323, 909(t)
emergency use of, 437–438
for arrhythmias, 323, 909(t)
in dog, 315(t)
for cardiopulmonary arrest, 437–438
for ventricular fibrillation, 909(t)
recommended dosages of, for dog, 909(t)
Brock procedure (modified), for pulmonic stenosis, 869–870
Bronchi, collapse of, 121
Bronchodilators, for pulmonary edema, 259–260, 260(t)
Bull terrier. See also *Dog(s).*
aortic stenosis in, gross morphology of, *488*
Bulldog. See also *Dog(s).*
echocardiography in, cardiac tumor on, *166*
pulmonic stenosis on, *486*
Bumetanide, for heart failure, 909(t)
Bundle branch block, *84,* 84–85, *85*
Butorphanol, adverse effects of, 909(t)
analgesic dosages of, 909(t)
cough-suppressant dosages of, 904(t), 909(t)
for tussive syncope, in dog, 453
recommended dosages of, for cat, 909(t)
for dog, 904(t), 909(t)
with acepromazine, for anxiety, in cat with pulmonary edema, 260, 260(t)
Butyrophenones, as preanesthetic agents, 858(t), 859(t), 860
Bypass tract–mediated macro-re-entrant tachycardia, in dog, 347, 355

Cachexia, cardiac, 47, *48,* 744–745
Cage rest, for dog with heartworm disease, 714–715
Calcium balance, disturbances of. See *Calcium deficit; Calcium excess.*
Calcium channel blockers. See also specific agents, e.g., *Diltiazem.*
adverse effects of, 315(t), 325
and hypotension, in dog, 351
drugs interacting with, effects of, 326(t)
for arrhythmias, 315(t), 324
in cat, 393
in dog, 348, 352
for atrial fibrillation, in dog, 352
for HCM, 218
for heart failure, 237(t), 238, 244–245
for hypertension, 805(t), 808
recommended dosages of, for cat, 903(t)
for dog, 903(t)
risks of use of, in therapy for myocardial infarction, in cat, 635, 639
Calcium deficit, 769
electrocardiographic characteristics of, *768,* 769, *784*
post-thyroidectomy, in cat, 788–789
electrocardiographic characteristics of, *784*
Calcium excess, 768–769
electrocardiographic characteristics of, 768, *768*
Calcium gluconate, emergency use of, 431(t), 438
for hypocalcemia, in thyroidectomized cat, 789
Calcium ipodate, for hyperthyroidism, 787
Cancer, cardiac. See *Heart, tumors of.*
chemotherapy for, cardiotoxicity of, in cat, 657
in dog, 609
Canine breed predisposition. See also *Dog(s).*
to arrhythmias, 465–466
to cardiogenic syncope, 451(t)
to chronic valvular heart disease, 463, 463(t)
to congenital heart disease, 459(t)–461(t), 463(t), 472(t)
to dilated cardiomyopathy, 582(t), 582–583, *583, 584*
to endocardiosis, 463, 463(t), 540, *541.* See also *King Charles spaniel, endocardiosis in.*
to respiratory disease, 43(t)
to sick sinus syndrome, 355, 466
to valvular heart disease, 459(t)–461(t), 460, 461, 462, 463, 463(t)
Captopril, adverse effects of, 909(t)
for HCM and myocardial infarction, in cat, 635
for heart failure, 241, 909(t)
Captopril *(Continued)*
for hypertension, 805(t), 909(t)
for myocardial infarction, in cat with hypertrophic cardiomyopathy, 635
recommended dosages of, for cat, 903(t), 909(t)
for dog, 903(t), 909(t)
Carbenicillin, for endocarditis, 577(t)
Carbimazole, for hyperthyroidism, 787
Carbon dioxide partial pressure, monitoring of, in CPCR, 441
Cardiac cachexia, 47, *48,* 744–745
Cardiac catheterization, 173–180
anesthesia for, 174
balloon dilation via, for pulmonic stenosis, 190, 868
coil occlusion via, for patent ductus arteriosus, 190
in dog, 511, *512*
complications associated with, 180
conditions contraindicating, 174
electrophysiologic applications of, 190
equipment for, 174, 175, *176,* 177
guidewires used in, 177
hemodynamic monitoring via. See *Hemodynamic monitoring.*
imaging during. See *Angiocardiography.*
indications for, 173–174
interventional, 866–867
for patent ductus arteriosus, 190
in dog, 511, *512*
for pulmonic stenosis, 190
left-sided, 177, *178,* 179–180
patient preparation for, 174
right-sided, 177, *178*
percutaneous (Seldinger) approach to, 174–175
valvuloplasty via, for pulmonic stenosis, 190
vascular cutdown facilitating, 175
Cardiac cycle, 33–35, *34*
Cardiac disease. See *Heart disease(s).*
Cardiac jelly, 4
Cardiac loop. See also *Heart.*
formation of, 3–4, *4*
development following, 4, *5*
Cardiac massage, in basic life support, 434–435
Cardiac output, 184
high, anemia and, 789
arteriovenous fistula and, 790
conditions causing, 781–791
heart failure in presence of, 781
hyperkinetic conditions and, 781
hypermetabolic conditions and, 781
hyperthyroidism and, 782
low, heart failure in presence of, 225
measurement of, 183–186, *185*
Cardiac silhouette, *108,* 111(t). See also *Cardiomegaly.*
Cardiac tamponade, 689–690
echocardiographic findings associated with, 164
in dog, *165*
pathophysiology of, *689,* 689–690, *690*
pericardial effusion and. See *Pericardial effusion.*
pericardiocentesis for, 694–695
Cardiac ultrasonography. See *Echocardiography.*
Cardiac valve(s). See *Heart, valve(s) of.*
Cardiogenic pulmonary edema. See *Heart failure.*
Cardiogenic shock, 272–273, 273(t). See also *Shock.*
Cardiogenic syncope, 446, 450–452

Cardiogenic syncope *(Continued)*
canine breed predisposition to, 451(t)
Cardiomegaly, 111–117, *112*
congenital heart disease and, 474–475
dilated cardiomyopathy and. See also *Dilated cardiomyopathy.*
in cat, *648*
in dog, *256,* 591, *591, 592*
electrocardiographic findings associated with, 77–80, *78–80*
endocardiosis and, *113*
hypertrophic cardiomyopathy and, in cat, *114, 115, 258,* 630, *631*
in dog, 604, *605*
restrictive cardiomyopathy and, in cat, 644
thromboembolism and, in cat, 661
tricuspid regurgitation and, 557
in dog, *114*
Cardiomyopathy (cardiomyopathies), 581–612, 621–658
arrhythmias associated with, in cat, 387, 387(t)
in dog, 369
congestive. See *Dilated cardiomyopathy.*
dilated. See *Dilated cardiomyopathy.*
Duchenne's, in dog, 607, *607,* 832
echocardiographic findings associated with, 161–163
in cat, 633–634, 644, 648–649
in dog, 591–594, 605, 607
electrocardiographic findings associated with, in cat, 630, 631(t), 643–644, 648
in dog, 590(t), 590–591, 605
heart failure and arrhythmias associated with, in cat, 387, 387(t)
in cat, 621–658
in dog, 581–612, 582(t)
infiltrative, 698. See also *Heart, tumors of.*
in cat, 657, *657, 688, 694*
in dog, 610
ischemic. See *Ischemia, myocardial.*
prevalence of, in cat, 465
in dog, 464–465
radiographic findings associated with, in cat, 630, *631, 632,* 644, 648, *648*
in dog, 591, *591, 592,* 604, *605*
restrictive. See *Restrictive cardiomyopathy.*
right ventricular, in cat, 653–655, *654, 655,* 831–832
in dog, 609
in man, 608–609
uremic, 770
weight ratios affected by, in cat, 847(t)
Cardiopulmonary arrest, 427–428
Cardiopulmonary cerebral resuscitation, 427–441
advanced life support in, 435–437, *436*
basic life support in, 429, 431–435, *432*
defibrillation in, 438–439
drugs used in, 431(t), 437–438
routes of administration for, 435–437
equipment for, 429
monitoring in, 439–441
personnel for, 428
readiness for, 428–429
checklist establishing, 430(t)
Cardiopulmonary diseases, 759–762
Cardioselectivity, of beta-adrenergic blocking agents, 311(t)
Cardiotoxicity, of chemotherapeutic agents, in cat, 657
in dog, 609
Cardiovascular disease. See also *Heart disease(s)* and specific conditions.
Cardiovascular disease *(Continued)*
diagnosis of, 41–64
angiocardiography in. See *Angiocardiography.*
auscultation in, 50–53, *51, 53.* See also *Heart murmurs; Heart sound(s).*
electrocardiography in. See *Electrocardiography.*
history in, 41–45, 42(t)
phonocardiography in. See *Phonocardiography.*
physical examination in, 46–64
radiography in. See *Radiography.*
specialized imaging techniques in, 193–200
ultrasonography in. See *Echocardiography.*
drugs for. See *Antiarrhythmic(s); Cardiovascular drugs.*
prevalence of, 457–468
signs of, 42–64, 43(t), 47(t)
interpretation of, *42*
surgery for. See *Surgery.*
Cardiovascular drugs. See also specific classes and agents.
body distribution of. See specifics cited under *Drug(s).*
emergency use of, 431(t), 437–438
routes for, 435–437
recommended dosages of, for cat and dog, 903(t)–917(t)
side effects of, 908(t)–917(t)
and hypotension, in dog, 351, *351*
and syncope, 453
Cardiovascular system. See also *Heart.*
anatomy of, 13–23
disorders of. See *Cardiovascular disease* and specific conditions.
physiology of, 25–36. See also *Heart, electrophysiology of.*
Cardioversion, in CPCR, 438–439
with antiarrhythmics. See *Antiarrhythmic(s).*
Carnitine, 746
deficiency of, 746–747
in cat, 748
in dog, and cardiomyopathy, 586, 747
Carnitine supplementation, for dog, 748, 909(t)
Carotid artery, left-sided cardiac catheterization via, *178,* 179. See also *Cardiac catheterization.*
Carotid sinus hypersensitivity, and syncope, 452
Carotid sinus massage, 450
in differentiation of tachyarrhythmias, in dog, 335–336, *339*
in provocative testing for syncope, 450
Carvedilol, for heart failure, 243
Cat(s). See also *Feline breed predisposition.*
acquired heart disease in. See also *Acquired heart disease.*
arrhythmias associated with, 387–388
prevalence of, 465
acromegaly in, 656
cardiovascular abnormalities associated with, 656
analgesics for, 854(t)
anesthetics for, 854(t), 858(t). See also *Anesthesia.*
angiocardiography in, *188*
DCM-related changes on, 649, *649*
HCM-related changes on, 630, *633, 662*
normal findings on, *188*
PDA-related findings on, *189*
Cat(s) *(Continued)*
RCM-related changes on, 644, *644*
signs of tetralogy of Fallot on, *514*
aortic embolism in. See under *Embolism.*
aortic stenosis in, gross morphology of, 823
aortic valve blood flow velocity in, Doppler-derived, 154(t)
arrhythmias in, 386–398. See also *Arrhythmia(s).*
acquired heart disease and, 387–388
cardiomyopathy and, 387, 387(t)
congenital heart disease and, 386–387
dilated cardiomyopathy and, 387(t)
treatment of, 650
electrocardiographic detection of, 389–390. See also *Cat(s), electrocardiography in.*
heart failure accompanying cardiomyopathy and, 387, 387(t)
hyperkalemia and, 388
hyperthyroidism and, 388
hypertrophic cardiomyopathy and, *387,* 387(t), 626, 630, 631(t), 635–636
myocardial diseases and, 387, 387(t)
potassium excess and, 388
restrictive cardiomyopathy and, 387(t)
supraventricular, 391–393
syncope associated with, 450, 451
thyrotoxicosis and, 388
treatment of, 315(t), 390, 392, 393, 394, 396, 397, 398
ventricular, 98, 99, 396–398, *397*
arrhythmogenic right ventricular dysplasia in, 653–655, *654, 655,* 831–832
arterial thromboembolism in, 658–667. See also *Thromboembolism.*
atrial extrasystoles in, 391, *391*
atrial fibrillation in, 392, *392*
atrial flutter in, 391–392
atrial septal defect in, gross morphology of, *495*
atrial tachycardia in, 391, *392*
atrioventricular block in, 82, *83,* 394–396, *395, 401*
as indication for pacemaker, 403
atrioventricular myopathy (persistent atrial standstill) in, 392, 658, 836
bacterial myocarditis in, *833*
blood pressure in, 796(t)
elevated, 468, 656–657, 797. See also *Hypertension.*
pharmacotherapy for, 805(t)
body weight loss in, 44
body weight of, ratio of heart weight to, 847(t)
as affected by cardiomyopathy, 847(t)
brachial artery embolization in, sequelae of, *660*
bradyarrhythmias in, 390, *401.* See also *Cat(s), bradycardia in.*
and syncope, 451
as indication for pacemaker, 400, 403
bradycardia in. See also *Cat(s), bradyarrhythmias in.*
sinus, 390
surgical anesthetic complications and, *92*
syncope associated with, 451
bundle branch block in, 84, 85
cancer chemotherapy in, cardiotoxicity of, 657
cardiac blood flow in, across valves, Doppler-derived velocity of, 154(t)
cardiac tumors in, 657, *657, 688,* 698–699, 836

Cat(s) *(Continued)*
echocardiographic findings associated with, *694*
prevalence of, 467
cardiomegaly in. See also *Cardiomegaly.*
dilated cardiomyopathy and, *648*
hypertrophic cardiomyopathy and, *114, 115, 258,* 630, *631*
restrictive cardiomyopathy and, 644
thromboembolism and, 661
cardiomyopathy in, 621–658, 622(t). See also *Cardiomyopathy (cardiomyopathies)* and specific types.
cardiovascular drug dosages for, 903(t)–917(t)
chemotherapeutic agents used in, cardiotoxicity of, 657
collapse of, syncopal. See *Cat(s), syncope in.*
color-flow Doppler echocardiography in, ventricular septal defect on, Plate 5
congenital heart disease in. See *Congenital heart disease.*
continuous-wave Doppler echocardiography in. See also *Cat(s), Doppler echocardiography in.*
hypertrophic cardiomyopathy on, *627*
mitral stenosis on, *136*
valvular stenosis on, *136*
dilated cardiomyopathy in, 645–652. See also *Dilated cardiomyopathy.*
dirofilariasis in, 727–734. See also *Heartworm disease.*
distal aortic embolism in. See under *Embolism.*
Doppler echocardiography in. See also *Cat(s), echocardiography in; Doppler echocardiography.*
aortic valve blood flow velocity derived from, 154(t)
hypertrophic cardiomyopathy on, *627,* 633–634
mitral stenosis on, *136*
mitral valve blood flow velocity derived from, 154(t), *624*
abnormal, *624*
pulmonic valve blood flow velocity derived from, 154(t)
tricuspid valve blood flow velocity derived from, 154(t)
valvular blood flow velocities derived from, 154(t)
valvular stenosis on, *136*
ventricular septal defect on, Plate 5
dysplastic right ventricle in. See *Cat(s), arrhythmogenic right ventricular dysplasia in.*
echocardiography in. See also *Echocardiography.*
aortic valve blood velocity derived from, 154(t)
cardiac tumor on, *694*
cardiomyopathy on, 633–634, 644, 648–649
dilated cardiomyopathy on, *648,* 648–649
dirofilariasis-related changes on, 731, *733*
heartworm-related changes on, 731, *733*
hypertrophic cardiomyopathy on, *626, 627, 629, 633,* 633–634
infiltrative cardiomyopathy on, *694*
left ventricular outflow tract obstruction on, hypertrophic cardiomyopathy and, *626, 627*

Cat(s) *(Continued)*
mitral regurgitation on, hypertrophic cardiomyopathy and, *627*
mitral stenosis on, *136*
mitral valve blood flow velocity derived from, 154(t), *624*
abnormal, *624*
normal findings on, 146(t)
pleural effusion on, *165, 168*
pulmonic valve blood velocity derived from, 154(t)
restrictive cardiomyopathy on, *643,* 644
"smoke" (spontaneous contrast) on, HCM and, *633*
tricuspid valve blood flow velocity derived from, 154(t)
valvular blood flow velocities derived from, 154(t)
valvular stenosis on, *136*
ventricular septal defect on, Plate 5
electrocardiography in, *75,* 75(t), 389–390. See also *Electrocardiography.*
arrhythmia detection via, 389–390
atrial extrasystoles on, 391, *391*
atrial fibrillation on, 392, *392*
atrial flutter on, 391
atrial tachycardia on, 391, *392*
atrioventricular block on, 82, *83,* 394–395, *395, 401*
bradyarrhythmias on, *401*
anesthesia-induced, *92*
bundle branch block on, 84, 85
cardiomyopathic changes on, 630, 631(t), 643–644, 648
DCM-related changes on, 648
fascicular block on, *85*
first-degree atrioventricular block on, 82
HCM-related changes on, 630, 631(t)
left atrial enlargement manifested on, 78
left bundle branch block on, 84
left ventricular enlargement manifested on, 79, 80, *80*
persistent atrial standstill on, 81, *81*
RCM-related changes on, 631(t), 643–644
right bundle branch block on, 85
right ventricular enlargement manifested on, 79
second-degree atrioventricular block on, *83, 401*
sinus bradycardia on, surgical anesthetic complications and, *92*
sinus nodal disturbances on, 390
sinus tachycardia on, hyperthyroidism and, 90, *90*
supraventricular arrhythmias on, 391
third-degree atrioventricular block on, *401*
thromboembolism manifested on, 661
ventricular arrhythmias on, 98, 99, 396, *397*
ventricular extrasystoles on, 396, *396*
ventricular pre-excitation on, *393,* 394
embolism in. See *Embolism, aortic; Thromboembolism, in cat.*
endocardial fibroelastosis in, 527, 652, 827
endocarditis in, infectious. See *Endocarditis, infectious.*
endomyocardial fibrosis in, 465, 831, *831*
endomyocardial form of RCM in, 641, 642, 643, *643.* See also *Restrictive cardiomyopathy.*
endomyocarditis in, 465, 832. See also *Endocarditis* and *Myocarditis.*

Cat(s) *(Continued)*
excessive left ventricular moderator bands in, 465, 655–656, *656,* 827
heart failure associated with, 832
fascicular block in, *85*
fibrillation in, atrial, 392, *392*
first-degree atrioventricular block in, 82, 394, *395*
flutter (atrial flutter) in, 391–392
growth hormone excess in, 656
cardiovascular abnormalities associated with, 656
heart disease in. See *Heart disease(s).*
heart failure in. See *Heart failure.*
heart sounds/heart murmurs in, hypertrophic cardiomyopathy and, 628, 630, *630*
heart weight to body weight ratio in, 847(t)
as affected by cardiomyopathy, 847(t)
heartworm disease in, 727–734. See also *Heartworm disease.*
hemorrhage in, secondary to warfarin therapy, 665, *665*
hypereosinophilic syndrome in, 643
hyperkalemia in, arrhythmias associated with, 388
reperfusion of ischemic limb and, 666
hypersomatotropism in, 656
cardiovascular abnormalities associated with, 656
hypertension in, 468, 656–657, 797. See also *Hypertension.*
pharmacotherapy for, 805(t)
hyperthyroidism in. See *Hyperthyroidism.*
hypertrophic cardiomyopathy in, 624–641. See also *Hypertrophic cardiomyopathy.*
hypokalemia in, potassium supplements countering, 915(t)
idiopathic myocardial failure in, 631(t), 645–652. See also "in cat" sub-subentries under *Dilated cardiomyopathy.*
infectious endocarditis in. See *Endocarditis, infectious.*
infectious peritonitis in, pericardial lesions accompanying, *688*
infiltrative cardiomyopathy in, 657, *657, 688, 694*
intraventricular conduction abnormalities in, 398
jugular venous distention in, significance of, *48*
left atrial enlargement in, electrocardiographic findings associated with, 78
left bundle branch block in, 84
left ventricular enlargement in, electrocardiographic findings associated with, 79, 80, *80*
left ventricular outflow tract obstruction in, hypertrophic cardiomyopathy and, 626, *626, 627*
treatment of, 639
limb contracture in, HCM-related thromboembolism and, *663*
limb paralysis in, amputation in management of, 665, *666*
dilated cardiomyopathy and, 647
hypertrophic cardiomyopathy and, 628, *660*
reperfusion following, complicated by hyperkalemia, 666
thromboembolism and, 44, 660, *660*
low-sodium diet for, 741(t). See also *Low-sodium diet.*
lymphosarcoma in, 836

Cat(s) *(Continued)*
and infiltrative cardiomyopathy, *657, 688, 694*
mid–left ventricular gradient in, hypertrophic cardiomyopathy and, 627
mitral regurgitation in. See also *Mitral regurgitation.*
hypertrophic cardiomyopathy and, 627, *627*
mitral stenosis in, echocardiographic findings associated with, *136*
pathology of, 823
mitral valve blood flow velocity in, Doppler-derived, 154(t), *624*
abnormal, *624*
M-mode echocardiography in. See also *Cat(s), echocardiography in.*
hypertrophic cardiomyopathy on, *626, 627*
normal findings on, 146(t)
pleural effusion on, *168*
Mobitz-type atrioventricular block in, *83,* 395, *395*
myocardial disease in, 621–658, 622(t). See also *Cardiomyopathy (cardiomyopathies)* and specific types.
myocardial form of RCM in, 641, 642, *642.* See also *Restrictive cardiomyopathy.*
myocardial infarction in, hypertrophic cardiomyopathy and, 635, 837, *838*
myocardial ischemia in, hypertrophic cardiomyopathy and, 625–626
myocarditis in, 657, *657, 820,* 832, *833.* See also *Cat(s), endomyocarditis in.*
ostium primum–type atrial septal defect in, gross morphology of, *495*
ostium secundum–type atrial septal defect in, gross morphology of, *495*
pacemaker for. See *Pacemaker.*
patent ductus arteriosus in, angiocardiographic findings associated with, *189*
pericardial disease in, 466, 679, 681–698, *683, 688.* See also *Pericardial* entries.
peritonitis in, infectious, pericardial lesions accompanying, *688*
persistent atrial standstill (atrioventricular myopathy) in, 392, 658, 836
electrocardiographic characteristics of, 81, *81*
persistent right aortic arch in, *528*
phonocardiography in, HCM-related changes on, *630*
pleural effusion in, dilated cardiomyopathy and, *648*
echocardiographic findings associated with, *165, 168*
radiographic findings associated with, *648*
potassium excess in, arrhythmias associated with, 388
reperfusion of ischemic limb and, 666
potassium supplements for, 915(t)
preanesthetic drugs for, 858(t). See also *Anesthesia.*
pulmonary edema in. See also *Pulmonary edema.*
anxiety reduction in treatment of, 260, 260(t)
heart failure and, *258*
hypertrophic cardiomyopathy and, *258,* 628, 630, *632*
treatment of, 261, 637–638
radiographic findings associated with, 258, *258*
pulmonic stenosis in, pathology of, 823. See also *Pulmonic stenosis.*

Cat(s) *(Continued)*
pulmonic valve blood flow velocity in, Doppler-derived, 154(t)
radiography in. See also *Radiography.*
cardiomegaly on, dilated cardiomyopathy and, *648*
hypertrophic cardiomyopathy and, *258,* 630, *631*
restrictive cardiomyopathy and, 644
thromboembolism and, 661
cardiomyopathic changes on, 630, *631, 632,* 644, 648, *648*
DCM-related changes on, 648, *648*
dirofilariasis-related changes on, 123, 731, *731*
features of heart failure on, *258*
HCM-related changes on, *114, 115, 258,* 630, *631, 632*
heartworm-related changes on, 123, 731, *731*
pleural effusion on, dilated cardiomyopathy and, *648*
pulmonary edema on, 258
HCM and, 630, *632*
heart failure and, *258*
hypertrophic cardiomyopathy and, *258*
RCM-related changes on, 644
thoracic conformation on, 110
renal infarction in, thromboembolism and, *661*
reperfusion syndrome in, hyperkalemia due to, 666
restrictive cardiomyopathy in, 641–645. See also *Restrictive cardiomyopathy.*
right bundle branch block in, 84
right ventricular cardiomyopathy in, 653–655, *654, 655,* 831–832
right ventricular enlargement in, electrocardiographic findings associated with, 79
right ventricular outflow tract obstruction in, hypertrophic cardiomyopathy and, 628
second-degree atrioventricular block in, *83,* 394–395, *395, 401*
sedatives for, 854(t)
sinus bradycardia in, 390
surgical anesthetic complications and, *92*
sinus nodal disturbances in, 390
sinus tachycardia in, 390
hyperthyroidism and, 90, *90*
sodium-restricted diet for, 741(t). See also *Sodium-restricted diet.*
subaortic stenosis in, gross morphology of, 823
supraventricular arrhythmias in, 391–393, *392*
syncope in. See also *Syncope.*
bradyarrhythmias and, 451
hypertrophic cardiomyopathy and, 636
tachyarrhythmias and, 450
systemic hypertension in, 656–657
tachyarrhythmias in. See also *Cat(s), arrhythmias in.*
hyperthyroidism and, 783(t), 786
hypertrophic cardiomyopathy and. See under *Arrhythmia(s), hypertrophic cardiomyopathy and.*
supraventricular, 391–393
syncope associated with, 450
ventricular, 98, 99, 396–398, *397*
tachycardia in, atrial, 391, *392*
sinus, 390
hyperthyroidism and, 90, *90*

Cat(s) *(Continued)*
supraventricular, 391, *392*
ventricular, 397–398
taurine deficiency in, and dilated cardiomyopathy, 645–646, 750–751
supplements countering, 637, 650, 751, 916(t)
tetralogy of Fallot in, angiocardiographic findings associated with, *514*
pathology of, 826
third-degree atrioventricular block in, 395, *395, 401*
as indication for pacemaker, 403
thrombosis in, 658–667. See also *Thromboembolism, in cat.*
thyrotoxic heart disease in. See *Thyrotoxic heart disease.*
tricuspid valve blood flow velocity in, Doppler-derived, 154(t)
two-dimensional echocardiography in, cardiac tumor on, *694*
dirofilariasis-related changes on, *733*
heartworm-related changes on, *733*
hypertrophic cardiomyopathy on, *626, 627, 629, 633*
mitral regurgitation on, hypertrophic cardiomyopathy and, *627*
pleural effusion on, *165*
restrictive cardiomyopathy on, *643*
spontaneous contrast ("smoke") on, hypertrophic cardiomyopathy and, *633*
vagal maneuvers in, aiding diagnosis of arrhythmias, 389
valvular heart disease in, *136,* 462, 463, 823
ventricular arrhythmias in, 98, 99, 396–398, *397*
ventricular extrasystoles in, 396, *396,* 397, 398
ventricular pre-excitation in, *393,* 393–394
ventricular septal defect in, echocardiographic findings associated with, Plate 5
gross morphology of, *500*
ventricular tachyarrhythmias in, 98, 99, 396–398, *397*
ventricular tachycardia in, 397–398
weight loss in, 44
weight of, ratio of heart weight to, 847(t)
as affected by cardiomyopathy, 847(t)
Catecholamine-secreting tumors, 765–766
Catheterization, cardiac. See *Cardiac catheterization.*
central venous, in CPCR, 441
peripheral arterial, in CPCR, 441
in left-sided cardiac catheterization, 177, *178,* 179–180. See also *Cardiac catheterization.*
Caudal vena cava, 17
radiographic appearance of, interpretation of, 120
Caval syndrome, in dog with heartworm disease, 718–719
surgery for, 879
Cefaclor, for endocarditis, 577(t)
Cefazolin, for endocarditis, 577(t)
Cefotaxime, for endocarditis, 577(t)
Cefoxitin, for endocarditis, 577(t)
Cell death, 818(t)
myocardial, in heart failure, 818–819
Central cyanosis, 48–49
Central nervous system, diseases of, cardiac manifestations of, 772

Central nervous system *(Continued)*
syncope due to, 447, 452–453
Central venous catheterization, in CPCR, 441
Central venous pressure monitoring, in care of anesthetized patient, 863
in management of shock, 280
Cephalexin, for endocarditis, 577(t)
Cephalosporins, for endocarditis, 577(t)
for shock, 284(t), 285
Cerebrovascular accident, hypertension and, 802
Chagas' disease (trypanosomiasis), and myocarditis, 833
in dog, 611, *611, 833*
Chemodectoma, cardiac, echocardiographic findings associated with, in dog, *166, 694*
surgery for, 880
Chemotherapeutic agents, as cardiotoxins, in cat, 657
in dog, 609
Chest. See *Thoracic* entries.
Chloramphenicol, interaction of phenytoin with, effects of, 326(t)
Chlorothiazide, adverse effects of, 909(t)
for edema, 909(t)
for heart failure, 235(t), 237
for hypertension, 909(t)
for pulmonary edema, 909(t)
recommended dosages of, for cat, 909(t)
for dog, 909(t)
Chordae tendineae, 19–20
rupture of, and pulmonary edema, in dog, *261*
in association with endocardiosis, 553–554
Chronaxie, in programming of pacemaker, *404,* 405
Chronic acquired atrioventricular valve disease. See *Endocardiosis.*
Chronic obstructive pulmonary disease (COPD), 761
Chronotropic drugs, positive. See specific agents, e.g., *Atropine; Glycopyrrolate; Isoproterenol.*
Circulation, 26, *26.* See also *Blood flow.*
blood volume and, 25–27
fetal, 8, *8*
transition from, to blood flow in newborn animal, 8–9
in basic life support, 433–434
pulmonary, 251–252
Clearance, of drugs, 312
Clicks, systolic, 54
Clindamycin, for endocarditis, 577(t)
Closed-chest compression, in basic life support, 433–434
factors limiting effectiveness of, 434(t)
Coagulopathies, shock and, 287
Coarctation of aorta, 494
Cocker spaniel. See also *Dog(s).*
dilated cardiomyopathy in, 582(t), *583*
cardiomegaly accompanying, *591*
radiographic findings associated with, *591*
M-mode echocardiography in, normal findings on, 145(t)
Codeine, recommended dosages of, for dog, 904(t)
Coding, of pacemaker, 406, *407*
Coil embolization, for patent ductus arteriosus, 190
in dog, 511, *512*
Collapse, bronchial, 121
syncopal. See *Syncope.*
Collapse *(Continued)*
tracheal, radiographic appearance of, 121, *122*
Colloid solutions, 277, 278(t)
in management of shock, 277–279
Color-flow Doppler echocardiography, 139
applications of, 559, 574, Plate 3, Plates 5 to 10
Color M-mode echocardiography, Plate 4
Compliance, ventricular, 30, *31, 217,* 217–218
Compression, of abdomen, in basic life support, 434
of chest, in basic life support, 433–434
factors limiting effectiveness of, 434(t)
of descending aorta, in basic life support, 435
Computed electrocardiography, 102
Computed tomography, of heart, *199,* 199–200
Concentric myocardial hypertrophy, pressure overload and, 208, 758, 818
Conduction, ventriculoatrial, as complication of cardiac pacing, 412, *413,* 414
Conduction abnormalities, 100–101, *101,* 299–303
echocardiographic characteristics of, 80–86
intraventricular, 84–86
in cat, 398
Conduction blocks, 299–300. See also *Atrioventricular block.*
Conduction system of heart, 22, *301*
development of, 7
lesions of, 836
Conduit repair, in surgery for pulmonic stenosis, 872
Conduit shunts, for tetralogy of Fallot, 875
Congenital heart disease, 471–529. See also specific lesions, e.g., *Tetralogy of Fallot.*
angiocardiographic assessment of, 475
arrhythmias associated with, in cat, 386–387
canine breed predisposition to, 459(t)–461(t), 463(t), 472(t)
cardiomegaly in, 474–475
echocardiographic evaluation of, 154–160, 475–476
electrocardiographic findings associated with, 476
pharmacotherapy for, 485(t)
prevalence of, in cat, 462–463
in dog, 458–462, 459(t)
radiographic evaluation of, 127, 127(t), 474–475
Congenital pericardial disease, 681–685, 835. See also specific types, e.g., *Diaphragmatic hernia, pericardial/ peritoneopericardial.*
Congestive cardiomyopathy. See *Dilated cardiomyopathy.*
Congestive heart failure. See *Heart failure.*
Conn's disease (aldosteronism), 765
electrocardiographic findings in, 765, *765*
Constant rate infusion, dosing formula worksheet for, 917
Constrictive pericarditis, 696–698
in dog, 696–698
hemodynamic effects of, *680,* 696, *697, 698*
pathology of, 696, *696*
Continuous heart murmurs, 62
Continuous-wave Doppler echocardiography, 138–139
Continuous-wave Doppler echocardiography *(Continued)*
advantages of, 138–139
aortic regurgitation on, subaortic stenosis and, in dog, *490*
aortic stenosis on, in dog, *136, 490*
disadvantages of, 139
hypertrophic cardiomyopathy on, in cat, *627*
left-to-right shunt on, ventricular septal defect and, in dog, *504*
mitral regurgitation on, in dog, *137*
mitral stenosis on, in cat, *136*
pulmonic stenosis on, in dog, *136, 486*
subaortic stenosis on, in dog, *136, 490*
tricuspid valve dysplasia on, in dog, *158*
valvular stenosis on, in cat, *136*
in dog, *136*
ventricular septal defect on, in dog, *504*
Contracture, HCM-related thromboembolism and, in cat, *663*
Contrast echocardiography, 134, *134, 135*
atrial septal defect on, in dog, *134, 135*
COPD (chronic obstructive pulmonary disease), 761
Cor pulmonale, 759–761, *760*
heartworm disease and, in dog, 715
Cor triatriatum, 526–527, *527*
pathology of, 824
surgery for, 878–879
Corgi. See also *Dog(s).*
M-mode echocardiography in, normal findings on, 145(t)
Coronary artery(ies), 21
disease of, 837
left, 21
right, 21
Coronary sinus, 17, 21
Coronary vessels, blood flow through, 33–34, *34*
development of, 7
Corticosteroids, use of, in CPCR, 438
in management of shock, 285
in treating sequelae of heartworm disease, in dog, 714, 716, 718
Costocervical vein, right, *418*
pacemaker implantation via, 415, 417(t)
Cough, 43–44
heart disease and, 43(t)
lung disease and, 43(t)
syncope associated with, in dog, 453. See also *Syncope.*
"Cough drop" syncope (tussive syncope), in dog, 453. See also *Syncope.*
Cough suppressants, for dog, 904(t), 909(t), 912(t)
Countershock, for ventricular fibrillation, 438–439
CPCR. See *Cardiopulmonary cerebral resuscitation.*
CPR. See *Cardiopulmonary cerebral resuscitation.*
Cranial vena cava, 17
left, persistent, 529
in dog, *529*
Crossbred beagle. See also *Dog(s).*
echocardiography in, heartworm-related changes on, *711*
Cross-clamping, of descending aorta, in basic life support, 435
Crystalloid solutions, in management of shock, 276–277
Culture, blood sample as source of bacteria for, in diagnosis of infectious endocarditis, 575. See also *Endocarditis, infectious.*

Cushing's syndrome
(hyperadrenocorticism), 764–765
Cyanosis, 44, 48–49, Plate 1
Cyst(s), blood, in tricuspid valve,
prevalence of, in dog, 463–464
intrapericardial, 684–685, *685, 686*

DCM. See *Dilated cardiomyopathy.*
Death, cardiopulmonary arrest and, 428.
See also *Cardiopulmonary cerebral resuscitation.*
dilated cardiomyopathy and, in dog,
595(t), 599, *600,* 600(t)
supraventricular tachycardia and, in dog,
348
ventricular arrhythmias and, in dog, 356–
357, 370, 836
Deerhound. See also *Dog(s).*
dilated cardiomyopathy in, *583*
M-mode echocardiography in, normal
findings on, 145(t)
Defibrillation, in CPCR, 438–439
Degeneration, myxomatous, of
atrioventricular valves. See
Endocardiosis.
Delayed afterdepolarizations, 298–299, *300*
Descending aorta, compression or cross-
clamping of, in basic life support, 435
Dexamethasone, emergency use of, 431(t),
438
for sequelae of heartworm disease, in
dog, 716
Dextrans, 278, 278(t)
in management of shock, 278–279
Diabetes mellitus, 767–768
Diaphragmatic hernia, pericardial/
peritoneopericardial, 526, 682–684,
683
abnormalities accompanying, 835
age distribution of, in cats, *683*
in dogs, *683*
cysts associated with, 684
radiographic findings associated with,
118, 526, 683–684
in dog, *684*
Diastolic dysfunction, hypertrophic
cardiomyopathy and, in man, 625
therapeutic approach to, 217–218
Diastolic function, 622–623
abnormal. See *Diastolic dysfunction.*
assessment of, via Doppler echocardiogra-
phy, 623
effects of disease states on, 623. See also
Diastolic dysfunction.
Diastolic heart murmurs, 61–62. See also
Heart murmurs.
Diastolic heart sounds, early, 55
Diet, mineral content of, as provided in
commercial dog foods, 742(t)–743(t)
sodium-restricted, in management of
heart failure, 237, 551
International Small Animal Cardiac
Health Council recommenda-
tions regarding, 905(t)
in management of hypertension, 745,
805–806
Diethylcarbamazine, for heartworm disease,
in dog, 720–721
Digitalis preparations, 325
adverse effects of, 315(t), 325, 744,
910(t)
in dog, *97,* 352
electrocardiographic parameters affected
by, 311(t), 325, *353*

Digitalis preparations *(Continued)*
for arrhythmias, 325, 910(t)
in cat, 315(t), 393
in cat with hypertrophic cardiomyopa-
thy, 636
in dog, 315(t), 349, 350, 352
evidence of effectiveness of, on ECG,
353
in dog with dilated cardiomyopathy,
598
evidence of effectiveness of, on ECG,
353
for atrial fibrillation, in dog, 352
evidence of effectiveness of, on ECG,
353
for DCM and arrhythmias, in dog, 598
evidence of effectiveness of, on ECG,
353
for DCM and heart failure, in cat, 651
in dog, 597
for HCM and arrhythmias, in cat, 636
for HCM and heart failure, in cat, 637,
641
for heart failure, 224, 229(t), 229–233,
485(t), 910(t)
in cat, 260(t)
in cat with dilated cardiomyopathy, 651
in cat with hyperthyroidism, 786
in cat with hypertrophic cardiomyopa-
thy, 637, 641
in dog, 260(t)
in dog with dilated cardiomyopathy,
597
in dog with mitral regurgitation, 551–
552
International Small Animal Cardiac
Health Council recommendations
regarding, 905(t)
for mitral regurgitation and heart failure,
in dog, 551–552
for supraventricular tachyarrhythmias, in
cat, 393
in dog, 349, 350
recommended dosages of, for cat, 904(t),
910(t)
for dog, 904(t), 910(t)
Dilated cardiomyopathy, 582–601
angiocardiographic findings associated
with, in cat, 649, *649*
radionuclide, in dog, *198*
arrhythmias accompanying, in cat, *387,*
387(t)
treatment of, 650
in dog, 369–370, 590, 590(t), 591
treatment of, 597, 598, 895–896
evidence of drug effectiveness in,
on ECG, *353*
"asymptomatic" early course of, in dog,
594–595
atrial fibrillation and, in dog, 588, 591
lethality of, *601*
breed predisposition to, among cats, *623*
among dogs, 582(t), 582–583, *583, 584*
canine, 582–601
cardiomegaly associated with, in cat, *648*
in dog, *256,* 591, *591, 592*
carnitine deficiency and, in dog, 586, 747
clinical manifestations of, in cat, 647–649
in dog, 588–589
compensation for, 207(t)
early "asymptomatic" course of, in dog,
594–595
echocardiographic findings associated
with, 162
in cat, *648,* 648–649
in dog, 591–594, *593*

Dilated cardiomyopathy *(Continued)*
electrocardiographic findings associated
with, in cat, 648
in dog, 590(t), 590–591
in dog with episodic weakness, *449*
in dog without overt signs of disease,
594–595, 595(t)
etiopathogenesis of, in cat, 645–646
in dog, 585–587
feline, 645–652
genetic/familial basis for, in dog, 585
in man, 585
heart failure demonstrable with, in dog,
892–893
heart failure potentiating lethality of, in
dog, *601*
heart failure treatment in, 223, 224, 225–
227
for cat, 649, 650, 651, 652
for dog, 596, 597, 894, 895
heart sounds and murmurs associated
with, in dog, *56,* 589
immune-mediated disorders and, in dog,
587
in man, 587
laboratory findings associated with, in
dog, 589
lethality of, in dog, 595(t), 599, *600,*
600(t)
limb paralysis accompanying, in cat, 647
"occult," in dog, 594–595
pathology of, in cat, 646, *647*
in dog, 583–585, *584, 819*
pathophysiology of, in cat, 646
in dog, 587–588
phonocardiographic findings associated
with, in dog, *56*
physical findings associated with, in dog,
589
precursors of, in dog, 594–595, 595(t)
prevalence of, in cat, *623,* 645
in dog, 582(t), 582–583, *583, 584*
prognosis associated with, in cat, 652
in dog, 599–601, *600,* 600(t), *601*
pulmonary edema accompanying, treat-
ment of, 223–224. See also *Dilated cardiomyopathy, heart failure treatment in.*
in dog, 261–262
radiographic findings associated with, in
cat, 648, *648*
in dog, *256,* 591, *591, 592*
tachycardia and, in dog, 587
taurine deficiency and, in cat, 645–646,
750–751
in dog, 585–586, 751–752
supplements countering. See *Taurine, supplemental.*
therapy for, in cat, 649–652
in dog, 596–599
in man, 652
thromboembolism associated with, in cat,
658. See also *Thromboembolism.*
viral etiology of, in man, 586
Diltiazem, 324–325
adverse effects of, 315(t), 325, 910(t)
and hypotension, in dog, *351*
drugs interacting with, effects of, 326(t)
electrocardiographic parameters affected
by, 311(t), *349*
for arrhythmias, 324, 910(t)
in cat, 315(t), 393
in dog, 315(t), 348, 349
evidence of effectiveness of, on ECG,
349
for HCM, in cat, 636, 639

Diltiazem *(Continued)*
for heart failure, 244–245
International Small Animal Cardiac Health Council recommendations regarding, 905(t)
for hypertension, 805(t)
for supraventricular tachyarrhythmias, in cat, 393
in dog, 348, 349
evidence of effectiveness of, on ECG, *349*
recommended dosages of, for cat, 903(t), 910(t)
for dog, 903(t), 910(t)
Dirofilaria immitis. See also *Heartworm disease.*
life cycle of, 702
Dirofilariasis. See *Heartworm disease.*
Dislodgment, of pacemaker leads, 415, 417, 419, *420*
Disopyramide, 316–317
adverse effects of, 315(t), 317, 910(t)
for arrhythmias, 316
in dog, 315(t), 910(t)
Disseminated intravascular coagulopathy, shock and, 287
Distributive shock, 273, 273(t). See also *Shock.*
Diuretics. See also specific agents.
for DCM and heart failure, in cat, 649, 651
in dog, 596, 597
for HCM and heart failure, in cat, 637, 638, 641
for heart failure, 235(t), 235–237
in cat with dilated cardiomyopathy, 649, 651
in cat with hypertrophic cardiomyopathy, 637, 638, 641
in cat with mitral regurgitation, 551
in dog with dilated cardiomyopathy, 596, 597
in dog with mitral regurgitation, 551
for hypertension, 805(t), 806
for mitral regurgitation and heart failure, in dog or cat, 551
for pulmonary edema, 259, 909(t), 912(t). See also *Diuretics, for heart failure.*
recommended dosages of, for cat, 903(t)
for dog, 903(t)
Doberman pinscher. See also *Dog(s).*
"asymptomatic" early course of DCM in, 594–595
atrial septal defect in, echocardiographic findings associated with, *496*
cardiomegaly in, dilated cardiomyopathy and, *592*
dilated cardiomyopathy in, 369–370, 582(t), *583, 584*
cardiomegaly accompanying, *592*
echocardiographic findings associated with, *593*
electrocardiographic findings associated with, 590, 590(t)
electrocardiographic findings predictive of, 594–595, 595(t)
histologic findings associated with, *584*
lethality of, 595(t), 599, 600(t)
pathology of, *584, 819*
precursors of, 594–595, 595(t)
radiographic findings associated with, *592*
early "asymptomatic" course of DCM in, 594–595
echocardiography in, atrial septal defect on, *496*

Doberman pinscher *(Continued)*
dilated cardiomyopathy on, *593*
electrocardiography in, DCM-related changes on, 590, 590(t)
DCM risk prediction based on, 594–595, 595(t)
M-mode echocardiography in, dilated cardiomyopathy on, *593*
"occult" dilated cardiomyopathy in, 594–595
ostium primum–type atrial septal defect in, echocardiographic findings associated with, *496*
radiography in, cardiomegaly on, dilated cardiomyopathy and, *592*
Dobutamine, 233–234
adverse effects of, 910(t)
for DCM and heart failure, in cat, 650
in dog, 596
for heart failure, 224, 229(t), 234, 260(t), 910(t)
in anemic animal, 790
in cat with dilated cardiomyopathy, 650
in dog with dilated cardiomyopathy, 596
for shock, 283, 283(t)
recommended dosages of, for cat, 904(t), 910(t)
for dog, 904(t), 910(t)
Dog(s). See also *Canine breed predisposition.*
abdominal ultrasonography in, signs of heart failure on, *153*
acquired heart disease in, 463–465. See also *Dog(s), endocardiosis in.*
analgesics for, 854(t)
anesthetics for, 854(t), 858(t). See also *Anesthesia.*
angiocardiography in, *188*
aortic stenosis on, *189*
evidence of double-chambered right ventricle on, *481*
mitral valve dysplasia on, *189, 525*
normal findings on, *188*
PDA-related findings on, *508*
pulmonic stenosis on, *189, 484*
radionuclide, *194*
ventricular abnormalities on, *194, 198*
subaortic stenosis on, *189*
tetralogy of Fallot on, *189, 514*
VSD-related findings on, *189, 501, 502*
aortic regurgitation in, 61
heart murmur associated with, 61
subaortic stenosis and, echocardiographic findings associated with, *490*
aortic stenosis in, 60. See also *Aortic stenosis.*
angiocardiographic findings associated with, *189*
echocardiographic evidence of, *136*, 159, *159, 490, 491, 492,* Plate 4
electrocardiographic findings associated with, *489*
gross morphology of, 486–487, *488*, 822–823
heart murmur associated with, *60*, 60–61
prevalence of, 459(t), 460
radiographic findings associated with, *491*
aortic valve blood flow velocity in, Doppler-derived, 154(t)
arrhythmias in, 331–375. See also *Arrhythmia(s).*
breed predisposition to, 465–466

Dog(s) *(Continued)*
dilated cardiomyopathy and, 369–370, 590, 590(t), 591
treatment of, 597, 598, 895–896
evidence of drug effectiveness in, on ECG, *353*
electrocardiographic detection of, 331–332. See also *Dog(s), electrocardiography in.*
frequency of, by type, 458(t), 465–466
heart failure and, 224
treatment of, 224
junctional, *97*, 346–347
sinus, *92*
supraventricular. See *Dog(s), supraventricular tachyarrhythmias in.*
syncope associated with, 450, 451
treatment of, 315(t), 347–355
management of dilated cardiomyopathy and, 597, 598
ventricular, 98, 99, *99*, 355–361
lethality of, 356–357, 370, 836
vs. supraventricular arrhythmias. See *Dog(s), supraventricular tachyarrhythmias in, differentiation of.*
arrhythmogenic right ventricular dysplasia in, 609
"asymptomatic" early course of DCM in, 594–595
atrial extrasystoles in, *94*
atrial fibrillation in, *95*, 343, *343, 344*, 345, *401*
and dilated cardiomyopathy, 588, 591
lethality of, *601*
occurring asymptomatically, among large breeds, 466
temporary, 354
treatment of, 352, 354
evidence of drug effectiveness in, on ECG, *353*
atrial flutter in, *95, 342*, 342–343, *401*
treatment of, 352
evidence of drug effectiveness in, on ECG, *353*
atrial septal defect in. See also *Atrial septal defect.*
corrected, echocardiographic findings following, Plate 9
echocardiographic evidence of, *134, 135, 496,* Plates 7 & 8
electrocardiographic findings associated with, *499*
prevalence of, 459(t), 462
shunt(ing) accompanying, echocardiographic findings associated with, *134, 135*
atrial tachycardia in, ectopic, *341*, 341–342
treatment of, 350–351
atrioventricular block in, 82, *82, 83*, 375, *401*
as indication for pacemaker, 402
atrioventricular myopathy (persistent atrial standstill) in, 403, 466, 607–608, *608*, 836, *837*
electrocardiographic characteristics of, 81
hyperkalemia and, *89*
atrioventricular nodal re-entrant tachycardia in, 345–346, *346*
atrioventricular node–dependent supraventricular tachycardia in, 338, 345–347
treatment of, 354–355
atrioventricular node–independent supraventricular tachycardia in, 338–345

Dog(s) *(Continued)*
treatment of, 348–354
atrioventricular valve disease in, chronic acquired. See *Dog(s), endocardiosis in.*
dysplastic, echocardiographic findings associated with, *158*
automatic (ectopic) junctional tachycardia in, 346–347
bacterial endocarditis in, echocardiographic findings in, *164*
vegetative mass associated with, *164*
bacterial myocarditis in, 612
bidirectional shunt in, atrial septal defect and, echocardiographic findings associated with, *135*
blood pressure in, 796(t)
breed differences in, 797(t)
changes in, with aging, 796(t)
effect of pacemaker on, *412*
elevated, 468, 797. See also *Hypertension.*
pharmacotherapy for, 805(t)
body weight loss in, 44
heart failure and, 47, *48*
body weight of, ratio of heart weight to, 847(t)
Borrelia burgdorferi infection in, 612
and myocarditis, 612
bradyarrhythmias in, 371–375, *401*
and syncope, 451
as indication for pacemaker, 400, 402–403
bundle branch block in, 84, *84*, 85, *85*
bypass tract–mediated macro-re-entrant tachycardia in, 347, 355
cancer chemotherapy in, cardiotoxicity of, 609
cardiac blood flow in, across valves, Doppler-derived velocity of, 154(t)
cardiac cachexia in, 47, *48*
cardiac tamponade in, echocardiographic findings associated with, *165*
cardiac tumors in, 610, 686, *687, 688*, 698
computed tomographic appearance of, *199*
echocardiographic findings associated with, *166*, 693, *694*
prevalence of, 466
radiographic findings associated with, *692*
cardiomegaly in, *112*. See also *Cardiomegaly.*
dilated cardiomyopathy and, *256*, 591, *591, 592*
endocardiosis and, *113*
hypertrophic cardiomyopathy and, 604, *605*
tricuspid regurgitation and, *114*
cardiomyopathy in, 581–612, 582(t). See also *Cardiomyopathy (cardiomyopathies)* and specific types.
cardiovascular drug dosages for, 903(t)–917(t)
carnitine deficiency in, and dilated cardiomyopathy, 586, 747
carnitine supplementation for, 748, 909(t)
caval syndrome in, heartworm disease and, 718–719
Chagas' disease in, 611
and myocarditis, 611, *611, 833*
chemodectoma in, cardiac, echocardiographic findings associated with, *166, 694*
chemotherapeutic agents used in, cardiotoxicity of, 609

Dog(s) *(Continued)*
chronic acquired atrioventricular valve disease in. See *Dog(s), endocardiosis in.*
collapse of, syncopal. See *Dog(s), syncope in.*
color-flow Doppler echocardiography in, Plate 3, Plates 5 to 10
commercial foods for, mineral content of, 742(t)–743(t)
computed tomography in, cardiac tumor on, *199*
congenital heart disease in. See also *Congenital heart disease.*
breed predisposition to, 459(t)–461(t), 463(t), 472(t)
prevalence of, 458–462, 459(t)
constrictive pericarditis in, 696–698
hemodynamic effects of, *680*, 696, *697, 698*
pathology of, 696, *696*
continuous-wave Doppler echocardiography in. See also *Dog(s), Doppler echocardiography in.*
aortic regurgitation on, subaortic stenosis and, *490*
aortic stenosis on, *136, 490*
left-to-right shunt on, ventricular septal defect and, *504*
mitral regurgitation on, *137*
pulmonic stenosis on, *136, 486*
subaortic stenosis on, *136, 490*
tricuspid valve dysplasia on, *158*
valvular stenosis on, *136*
ventricular septal defect on, *504*
contrast echocardiography in. See also *Dog(s), echocardiography in.*
atrial septal defect on, *134, 135*
shunt(ing) on, atrial septal defect and, *134, 135*
cor pulmonale in, heartworm disease and, 715
cor triatriatum in, echocardiographic findings associated with, *527*
"cough drop" syncope (tussive syncope) in, 453. See also *Syncope.*
death of, supraventricular tachycardia and, 348
ventricular arrhythmias and, 356–357, 370
digitalis toxicity in, *97*, 352
dilated cardiomyopathy in, 582–601. See also *Dilated cardiomyopathy.*
dirofilariasis in, 702–721. See also *Heartworm disease.*
Doppler echocardiography in. See also *Dog(s), echocardiography in.*
aortic regurgitation on, subaortic stenosis and, *490*
aortic stenosis on, *136*
aortic valve blood flow velocity derived from, 154(t)
atrial septal defect on, *134, 135, 496*, Plates 7 & 8
atrioventricular valve dysplasia on, *158*
left-to-right shunt on, patent ductus arteriosus and, *156*
ventricular septal defect and, *504*
mitral regurgitation on, *137*, Plate 10
mitral valve blood flow velocity derived from, 154(t)
patent ductus arteriosus on, *156*
pulmonic stenosis on, *136*, 160, *486*
pulmonic valve blood flow velocity derived from, 154(t)
shunt(ing) on, patent ductus arteriosus and, *156*

Dog(s) *(Continued)*
subaortic stenosis on, *136*
tricuspid valve blood flow velocity derived from, 154(t)
tricuspid valve dysplasia on, *158*
valvular blood flow velocities derived from, 154(t)
valvular dysplasia on, *158*
valvular stenosis on, *136*, 160
ventricular septal defect on, *504*, Plate 6
double-chambered right ventricle in, angiocardiographic findings associated with, *481*
echocardiographic findings associated with, *481*
Duchenne's cardiomyopathy in, 607, *607*, 832
dyspnea in, signs accompanying, *47*
early "asymptomatic" course of DCM in, 594–595
echocardiography in, *133*. See also *Echocardiography.*
aortic regurgitation on, subaortic stenosis and, *490*
aortic stenosis on, *136*, 159, *159, 490, 491, 492*, Plate 4
aortic valve blood flow velocity derived from, 154(t)
atrial septal defect on, *134, 135, 496*, Plates 7 & 8
atrioventricular valve dysplasia on, *158*
bidirectional shunt on, atrial septal defect and, *135*
cardiac tamponade on, *165*
cardiac tumors on, *166*, 693, *694*
cardiomyopathy on, 591–594, 605, 607
chemodectoma on, cardiac, *166, 694*
cor triatriatum on, *527*
dilated cardiomyopathy on, 591–594, *593*
dirofilariasis-related changes on, 710, *711*
double-chambered right ventricle on, *481*
Duchenne's cardiomyopathy on, 607, *607*
endocardiosis and mitral regurgitation on. See *Dog(s), echocardiography in, mitral regurgitation on.*
evidence of endocarditis on, *164*
heartworm-related changes on, 710, *711*
hypertrophic cardiomyopathy on, 605, *606*
intrapericardial cyst on, *686*
left-to-right shunt on, patent ductus arteriosus and, *156, 510*
ventricular septal defect and, *504*
mitral regurgitation on, *137, 161*, Plate 10
mitral valve blood flow velocity derived from, 154(t)
muscular dystrophy–related myocardial lesions on, 607, *607*
normal findings on, *133*, 145(t)
ostium primum–type atrial septal defect on, *496*, Plate 8
ostium secundum–type atrial septal defect on, *134*
patent ductus arteriosus on, *156, 510*
pericardial cyst on, *686*
pericardial effusion on, *165, 167, 691, 693*
pleural effusion on, *165, 693*
pulmonic stenosis on, *136*, 160, *160, 486*, Plate 3

Dog(s) *(Continued)*
pulmonic valve blood flow velocity derived from, 154(t)
right atrial hemangiosarcoma on, *166, 694*
right-to-left shunt on, atrial septal defect and, *134*
right ventricle on, double-chambered, *481*
shunt(ing) on, atrial septal defect and, *134, 135*
patent ductus arteriosus and, *156*
sinus venosus–type atrial septal defect on, *135,* Plate 7
subaortic stenosis on, *136,* 159, *159, 490, 491, 492,* Plate 4
tetralogy of Fallot on, *516*
tricuspid valve blood flow velocity derived from, 154(t)
tricuspid valve dysplasia on, *158*
valvular blood flow velocities derived from, 154(t)
valvular dysplasia on, *158*
valvular stenosis on, *136,* 159, *159,* 160, *160*
vegetative mass on, endocarditis and, *164*
ventricular septal defect on, *157, 501, 502, 504,* Plate 6
ectopic atrial tachycardia in, *341,* 341–342
treatment of, 350–351
ectopic (automatic) junctional tachycardia in, 346–347
electrical alternans in, pericardial effusion and, *90, 691*
electrocardiography in, *75,* 75(t), 331–332. See also *Electrocardiography.*
antiarrhythmic drug effects evidenced on, *349, 350, 351, 353,* 361, *361*
arrhythmia detection via, 331–332
ASD-related findings on, *499*
atrial extrasystoles on, *94*
atrial fibrillation on, *95,* 343, *343, 344, 401*
atrial flutter on, *95,* 342, *342, 401*
atrioventricular block on, 82, *82, 83, 401*
atrioventricular nodal re-entrant tachycardia on, 345, *346*
bradyarrhythmias on, *401*
bundle branch block on, 84, *84,* 85, *85*
bypass tract–mediated macro-re-entrant tachycardia on, 347
cardiomyopathic changes on, 590(t), 590–591, 605
DCM risk prediction based on, 594–595, 595(t)
DCM-related changes on, *449,* 590(t), 590–591
digitalis-induced abnormalities on, *97*
ectopic atrial tachycardia on, 341, *341*
electrical alternans on, pericardial effusion and, *90, 691*
first-degree atrioventricular block on, 82, *82*
HCM-related changes on, 605
junctional arrhythmias on, *97,* 347
left atrial enlargement manifested on, 78, *78*
left bundle branch block on, 84, *84*
left ventricular enlargement manifested on, 79, 80
mitral valve dysplasia manifested on, *524*
pacemaker effects on, *404, 407, 408, 411, 413, 419–422, 424*

Dog(s) *(Continued)*
PDA-related findings on, *510*
pericardial effusion–related changes on, *691*
persistent atrial standstill on, 81
hyperkalemia and, *89*
right atrial enlargement manifested on, 77
right bundle branch block on, 85, *85*
right ventricular hypertrophy or enlargement manifested on, 78–79, *79, 482*
second-degree atrioventricular block on, *82, 401*
sick sinus syndrome on, 93, *93, 401*
sinoatrial block on, *81*
sinus nodal re-entrant tachycardia on, 339
sinus node tachycardia on, 338
subaortic stenosis manifested on, *489*
supraventricular tachyarrhythmias on, *96*
vs. ventricular tachyarrhythmias, 333–334, *333–338*
third-degree atrioventricular block on, *83, 401*
tricuspid valve dysplasia manifested on, *524*
ventricular extrasystoles on, *98*
ventricular pre-excitation on, *86*
ventricular tachyarrhythmias on, 98, 99, *99*
vs. supraventricular tachyarrhythmias, 333–334, *333–338*
VSD-related findings on, *504*
embolism in. See *Dog(s), thromboembolism in.*
endocardiosis in. See also *Endocardiosis.*
breed predisposition to, 463, 463(t), 540, *541.* See also *King Charles spaniel, endocardiosis in.*
heart murmur accompanying, 540, *541,* 544–545
intensity of, and severity of associated heart failure, *544, 545*
left atrial rupture as sequela of, *555*
mitral regurgitation associated with. See *Dog(s), mitral regurgitation in.*
neurohormonal response associated with, 542, *543*
pathology of, *539*
prognosis associated with, *553*
radiographic features of, *113*
endocarditis in, infectious, *569.* See also *Endocarditis, infectious.*
increased risk of, with aging, *568*
prevalence of, 464, 567, *568*
vegetative mass associated with, *164*
episodic weakness in. See also *Syncope.*
DCM and, electrocardiographic findings associated with, *449*
exercise-induced syncope in, 449. See also *Syncope.*
external cardiac anatomy of, 16, *16, 17.* See also *Heart.*
fibrillation in, atrial, *95,* 343, *343, 344,* 345, *401*
and dilated cardiomyopathy, 588, 591
lethality of, *601*
occurring asymptomatically, among large breeds, 466
temporary, 354
treatment of, 352, 354
evidence of drug effectiveness in, on ECG, *353*

Dog(s) *(Continued)*
first-degree atrioventricular block in, 82, *82,* 375
flutter (atrial flutter) in, *95, 342,* 342–343, *401*
treatment of, 352
evidence of drug effectiveness in, on ECG, *353*
fungal myocarditis in, 612
heart disease in. See *Heart disease(s).*
heart failure in. See *Heart failure.*
heart murmurs in. See also *Heart murmurs.*
dilated cardiomyopathy and, 589
endocardiosis and, 540, *541,* 544–545
correlated with severity of associated heart failure, *544, 545*
hypertrophic cardiomyopathy and, 604
patent ductus arteriosus and, *62*
valvular disease and, *59,* 60, *60,* 61, 62, *62*
heart weight to body weight ratio in, 847(t)
heartworm disease in, 702–721. See also *Heartworm disease.*
hemangiosarcoma in, right atrial, *166, 687, 694*
echocardiographic findings associated with, *166, 694*
highly digestible diet for, 741(t)
Holter monitoring in, 331–332. See also *Dog(s), electrocardiography in.*
hyperkalemia in, electrocardiographic findings associated with, *89*
hypertension in, 468, 797. See also *Hypertension.*
pharmacotherapy for, 805(t)
hypertrophic cardiomyopathy in, 601–606. See also *Hypertrophic cardiomyopathy.*
hypotension in, cardiovascular drug–induced, 351, *351*
immune-mediated disorders in, and dilated cardiomyopathy, 587
infectious endocarditis in, *569.* See also *Endocarditis, infectious.*
increased risk of, with aging, *568*
prevalence of, 464, 567, *568*
vegetative mass associated with, *164*
infectious myocarditis in, 465, 610–612, 832
infiltrative cardiomyopathy in, 610
interatrial septal defect in, prevalence of, 459(t), 462
internal cardiac anatomy of, *18.* See also *Heart.*
interventricular septal defect in, prevalence of, 459(t), 461
intrapericardial cyst in, *686*
intrapericardial pressure-volume relationships in, *680*
constrictive pericarditis and, *680*
pericardial effusion and, *680*
junctional arrhythmias in, *97,* 346–347
left atrial enlargement in, electrocardiographic findings associated with, 78, *78*
left atrial rupture in, endocardiosis and, *555*
left bundle branch block in, 84, *84*
left ventricular enlargement in, electrocardiographic findings associated with, 79, 80
left ventricular outflow tract obstruction in, hypertrophic cardiomyopathy and, treatment of, 606

Dog(s) *(Continued)*
left-to-right shunt in, patent ductus arteriosus and. See *Dog(s), patent ductus arteriosus in.*
ventricular septal defect and, echocardiographic findings associated with, *504*
low-sodium diet for, 741(t). See also *Low-sodium diet.*
lung disease in, breed predisposition to, 43(t)
dirofilariasis and, 716–718
treatment of, 714, 716, 718
vascular, prevalence of, 467
Lyme disease in, 612
and myocarditis, 612
lymphadenopathy in, appearance of, on radiography, *121*
lymphomatoid granulomatosis in, heartworm disease and, 718
macro-re-entrant tachycardia in, bypass tract–mediated, 347, 355
mitral regurgitation in. See also *Mitral regurgitation.*
echocardiographic findings associated with, *137, 161*
heart murmur accompanying, *59,* 60
magnetic resonance imaging of, *200*
pulmonary edema accompanying, treatment of, 261
radionuclide angiocardiographic findings associated with, *198*
mitral stenosis in, heart murmur accompanying, 61, *62*
pathology of, 823
mitral valve blood flow velocity in, Doppler-derived, 154(t)
mitral valve dysplasia in, angiocardiographic findings associated with, *189, 525*
electrocardiographic findings associated with, *524*
prevalence of, 459(t), 462
radiographic manifestations of, *523*
M-mode echocardiography in, *133.* See also *Dog(s), echocardiography in.*
aortic stenosis on, *491,* Plate 4
dilated cardiomyopathy on, *593*
dirofilariasis-related changes on, *711*
heartworm-related changes on, *711*
hypertrophic cardiomyopathy on, *606*
normal findings on, *133,* 145(t)
pericardial effusion on, *167, 691*
subaortic stenosis on, *491,* Plate 4
MRI in, mitral regurgitation on, *200*
muscular dystrophy in, 606–607, 832
myocardial lesions associated with, 607, *607*
mycotic myocarditis in, 612
myocardial disease in, 581–612, 582(t). See also *Cardiomyopathy (cardiomyopathies)* and specific types.
myocardial infarction in, 610
myocardial ischemia in, 610
myocarditis in, 465, 610–612, *611,* 832, *833*
neosporosis in, 611–612
"occult" dilated cardiomyopathy in, 594–595
occult heartworm disease in, 705–706
ostium primum–type atrial septal defect in, echocardiographic findings associated with, *496,* Plate 8
ostium secundum–type atrial septal defect in, echocardiographic findings associated with, *134*

Dog(s) *(Continued)*
pacemaker for. See *Pacemaker.*
patent ductus arteriosus in. See also *Ductus arteriosus, patent.*
angiocardiographic findings associated with, *508*
coil occlusion of, 511, *512*
echocardiographic findings associated with, *156, 510*
electrocardiographic findings associated with, *510*
interventional cardiac catheterization for, 511, *512*
pathology of, 824
phonocardiographic findings associated with, *62*
treatment of, 228, 511, *512*
complications of, 511, *512*
pericardial cyst in, *686*
pericardial effusion in. See also *Pericardial effusion.*
echocardiographic findings associated with, *165, 167, 691, 693*
effect of, on pericardial pressure-volume relationships, *680*
electrocardiographic findings associated with, *90, 691*
etiology of, 685–686
prevalence of, 466
radiographic appearance of, 118, *118*
tumors causing, 686
pericardial mesothelioma in, 686, *688*
pericardial/peritoneopericardial diaphragmatic hernia in, *683, 684.* See also *Diaphragmatic hernia, pericardial/peritoneopericardial.*
pericardial pressure-volume relationships in, *680*
constrictive pericarditis and, *680*
pericardial effusion and, *680*
pericarditis in, constrictive, 696–698
hemodynamic effects of, *680,* 696, *697, 698*
pathology of, 696, *696*
persistent atrial standstill (atrioventricular myopathy) in, 403, 466, 607–608, *608,* 836, *837*
electrocardiographic characteristics of, 81
hyperkalemia and, *89*
persistent left cranial vena cava in, *529*
persistent right aortic arch in, prevalence of, 459(t), 462
phonocardiography in, split second heart sound on, *55*
third heart sound on, abnormal, dilated cardiomyopathy and, *56*
pleural effusion in, echocardiographic findings associated with, *693*
potassium overload in, electrocardiographic findings associated with, *89*
preanesthetic drugs for, 858(t). See also *Anesthesia.*
protozoal myocarditis in, 611–612
pulmonary edema in. See also *Pulmonary edema.*
dilated cardiomyopathy and, *256*
treatment of, 261–262
heart failure and, *256, 257*
mitral regurgitation and, treatment of, 261
morphine for, anxiolytic effects of, 260, 260(t)
radiographic findings associated with, *256, 257,* 258, *259, 261*
ruptured chordae tendineae and, *261*

Dog(s) *(Continued)*
seizures and, *259*
pulmonic regurgitation in, and heart murmur, 62
pulmonic stenosis in, 823
angiocardiographic findings associated with, *189, 484*
echocardiographic evidence of, *136,* 160, *160, 486,* Plate 3
gross morphology of, 478, *479,* 480, 823
prevalence of, 459(t), 460–461
radiographic findings associated with, *482*
right ventricular hypertrophy accompanying, *482*
pulmonic valve blood flow velocity in, Doppler-derived, 154(t)
pulsed-wave Doppler echocardiography in. See also *Dog(s), Doppler echocardiography in; Dog(s), echocardiography in.*
mitral regurgitation on, *137*
patent ductus arteriosus on, *156*
pulmonic stenosis on, *486*
radiography in. See also *Radiography.*
aortic stenosis evidenced on, *491*
cardiac silhouette on, *108.* See also *Dog(s), radiography in, cardiomegaly on.*
cardiac tumor–related changes on, *692*
cardiomegaly on, *112*
dilated cardiomyopathy and, *256,* 591, *591, 592*
endocardiosis and, *113*
hypertrophic cardiomyopathy and, 604, *605*
tricuspid regurgitation and, *114*
cardiomyopathic changes on, 591, *591, 592,* 604, *605*
DCM-related changes on, *256,* 591, *591, 592*
dirofilariasis-related changes on, *117,* 123, *125,* 709–710, *710, 717,* 717–718
features of heart failure on, *256, 257*
HCM-related changes on, 604, *605*
heartworm-related changes on, *117,* 123, *125,* 709–710, *710, 717,* 717–718
intrapericardial cyst on, *686*
lymphadenopathy on, *121*
manifestations of mitral valve dysplasia on, *523*
pericardial cyst on, *686*
pericardial effusion on, 118, *118*
pericardial/peritoneopericardial diaphragmatic hernia on, *684*
pulmonary edema on, 258
dilated cardiomyopathy and, *256*
heart failure and, *256, 257*
noncardiogenic, *259*
ruptured chordae tendineae and, *261*
seizures and, *259*
right ventricular enlargement on, *117*
signs of pulmonic stenosis on, *482*
signs of subaortic stenosis on, *491*
small heart on, *111*
thoracic conformation on, *109,* 110
tracheal collapse on, *122*
tricuspid valve dysplasia manifested on, *114, 523*
VSD-related findings on, *503*
radionuclide angiocardiography in, *194*
ventricular abnormalities on, *194, 198*
re-entrant tachycardia in, atrioventricular nodal, 345–346, *346*

Dog(s) *(Continued)*
bypass tract–mediated, 347
sinus nodal, 339, 341
right atrial enlargement in, electrocardiographic findings associated with, 77
right atrial hemangiosarcoma in, *166, 687, 694,* 880
echocardiographic findings associated with, *166, 694*
right bundle branch block in, 85, *85*
right-to-left shunt in, ASD and, echocardiographic findings associated with, *134*
right ventricular cardiomyopathy in, 609
right ventricular enlargement in, electrocardiographic findings associated with, 78–79, *79*
radiographic appearance of, *117*
right ventricular hypertrophy in, electrocardiographic findings associated with, *482*
ruptured chordae tendineae in, and pulmonary edema, *261*
second-degree atrioventricular block in, *82,* 375, *401*
sedatives for, 854(t)
seizures in, pulmonary edema secondary to, *259*
shunt(ing) in, atrial septal defect and, echocardiographic findings associated with, *134, 135*
patent ductus arteriosus and. See *Dog(s), patent ductus arteriosus in.*
ventricular septal defect and, echocardiographic findings associated with, *504*
sick sinus syndrome in, 93, *93,* 402–403
breed predisposition to, 355, 466
electrocardiographic findings associated with, 93, *93, 401*
syncope accompanying, 450
tachycardia associated with, 355
sinoatrial block in, *81*
sinus arrhythmia in, *92*
sinus nodal re-entrant tachycardia in, 339, 341
sinus node tachycardia in, 338–339
sinus venosus–type atrial septal defect in, echocardiographic findings associated with, *135*
sodium-restricted diet for, 741(t). See also *Sodium-restricted diet.*
subaortic stenosis in. See *Dog(s), aortic stenosis in.*
supraventricular tachyarrhythmias in, 338–347
differentiation of, from ventricular tachyarrhythmias, 332(t), 332–338
P wave and QRS complex in, 333–334, *336, 337, 338*
QRS complex morphology in, 333, *333, 334, 335*
unreliability of rhythm (ir)regularities and pause length in, 334–335
vagal maneuvers in, 335–336, 338, *339, 340*
treatment of, 347–355
adverse effects of, 351–352
evidence of drug effectiveness in, on ECG, *349, 350, 351, 353*
supraventricular tachycardia in, *96,* 338–347. See also *Dog(s), supraventricular tachyarrhythmias in.*
AV node–dependent, 338, 345–347

Dog(s) *(Continued)*
treatment of, 354–355
AV node–independent, 338–345
treatment of, 348–354
death risk associated with, 348
F waves associated with. See *Dog(s), atrial fibrillation in; Dog(s), atrial flutter in.*
syncope in. See also *Syncope.*
bradyarrhythmias and, 451
breed predisposition to, 451(t)
exercise testing for, 449
sick sinus syndrome and, 450
tachyarrhythmias and, 450
tussive ("cough drop"), 453
vasovagal, 452
systemic vascular disease in, prevalence of, 467
tachyarrhythmias in, 338–347, 355–361. See also *Dog(s), tachycardia in.*
supraventricular. See *Dog(s), supraventricular tachyarrhythmias in.*
syncope associated with, 450
ventricular, 98, 99, *99,* 355–361
differentiation of, from supraventricular tachyarrhythmias. See *Dog(s), supraventricular tachyarrhythmias in, differentiation of.*
tachycardia in. See also *Dog(s), supraventricular tachyarrhythmias in.*
atrioventricular nodal re-entrant, 345–346, *346*
automatic (ectopic) junctional, 346–347
bypass tract–mediated macro-re-entrant, 347, 355
dilated cardiomyopathy associated with, 587
ectopic atrial, *341,* 341–342
treatment of, 350–351
ectopic (automatic) junctional, 346–347
heart failure associated with, 587
sick sinus syndrome and, 355
sinus nodal re-entrant, 339, 341
sinus node, 338–339
supraventricular. See *Dog(s), supraventricular tachycardia in.*
ventricular, 98, 99, *99*
taurine deficiency in, and dilated cardiomyopathy, 585–586
supplements countering, 596, 916(t)
temporary atrial fibrillation in, 354
tetralogy of Fallot in, angiocardiographic findings associated with, *189, 514*
echocardiographic findings associated with, *516*
pathology of, 826
prevalence of, 459(t), 462
third-degree atrioventricular block in, *83,* 375, *401*
as indication for pacemaker, 402
thromboembolism in, aspirin for, 908(t)
heparin for, as element of therapy for heartworm disease, 713, 715, 719
pulmonary, prevalence of, 467
warfarin for, 917(t)
toxoplasmosis in, and myocarditis, 611
tracheal collapse in, radiographic appearance of, *122*
tricuspid stenosis in, 823
tricuspid valve blood flow velocity in, Doppler-derived, 154(t)
tricuspid valve dysplasia in, echocardiographic findings associated with, *158*
electrocardiographic findings associated with, *524*

Dog(s) *(Continued)*
prevalence of, 459(t), 461–462
radiographic manifestations of, *114, 523*
trypanosomiasis in, 611
and myocarditis, 611, *611, 833*
tussive syncope ("cough drop" syncope) in, 453. See also *Syncope.*
24-hour electrocardiographic monitoring in, 331–332. See also *Dog(s), electrocardiography in.*
two-dimensional echocardiography in. See also *Dog(s), echocardiography in.*
aortic stenosis on, 159, *159, 492*
cardiac tamponade on, *165*
cardiac tumor on, *694*
cor triatriatum on, *527*
dilated cardiomyopathy on, *593*
dirofilariasis-related changes on, *711*
Duchenne's cardiomyopathy on, *607*
endocardiosis on, *161*
evidence of endocarditis on, *164*
heartworm-related changes on, *711*
hypertrophic cardiomyopathy on, *606*
intrapericardial cyst on, *686*
left-to-right shunt on, patent ductus arteriosus and, *156, 510*
mitral regurgitation on, endocardiosis and, *161*
muscular dystrophy–related myocardial lesions on, *607*
patent ductus arteriosus on, *156, 510*
pericardial cyst on, *686*
pericardial effusion on, *165, 693*
pleural effusion on, *165, 693*
pulmonic stenosis on, *160*
subaortic stenosis on, 159, *159, 492*
tetralogy of Fallot on, *516*
valvular stenosis on, 159, *159, 160*
vegetative mass on, endocarditis and, *164*
ventricular septal defect on, *157, 502*
vagal maneuvers in, aiding differentiation of tachyarrhythmias, 335–336, 338, *339, 340*
valvular heart disease in. See also valve-specific sub-entries, e.g., *Dog(s), mitral stenosis in.*
acquired, 463(t), 463–464. See also *Endocardiosis.*
breed predisposition to, 459(t)–461(t), 460, 461, 462, 463, 463(t)
congenital, 459(t)–461(t), 460–462, 463(t)
prevalence of, 459(t), 460–462, 463, 464
vascular disease in, pulmonary, prevalence of, 467
systemic, prevalence of, 467
vasovagal syncope in, 452. See also *Syncope.*
ventricular arrhythmias in, 98, 99, *99,* 355–361
lethality of, 356–357, 370, 836
vs. supraventricular arrhythmias. See *Dog(s), supraventricular tachyarrhythmias in, differentiation of.*
ventricular extrasystoles in, *98*
breed predisposition to, 466
ventricular pre-excitation in, *86*
ventricular septal defect in, angiocardiographic findings associated with, *189, 501, 502*
radionuclide, *194*
echocardiographic evidence of, *157, 501, 502, 504,* Plate 6

Dog(s) *(Continued)*
electrocardiographic findings associated with, *504*
prevalence of, 459(t), 461
radiographic findings associated with, *503*
ventricular tachyarrhythmias in, 98, 99, *99*, 355–361
vs. supraventricular tachyarrhythmias. See *Dog(s), supraventricular tachyarrhythmias in, differentiation of.*
viral myocarditis in, 610–611, 832
weakness in, episodic. See also *Syncope.*
DCM and, electrocardiographic findings associated with, *449*
weight loss in, 44
heart failure and, 47, *48*
weight of, ratio of heart weight to, 847(t)
X-linked muscular dystrophy in, 606–607, 832
myocardial lesions associated with, 607, *607*
Dog foods, commercial, mineral content of, 742(t)–743(t)
Dopamine, 233
adverse effects of, 911(t)
emergency use of, 438
for atrioventricular block, in cat, 396
for DCM and heart failure, in cat, 650
for heart failure, 224, 229(t), 233, 260(t), 911(t)
in cat with dilated cardiomyopathy, 650
for renal failure associated with shock, 286
for shock, 282–283, 283(t), 286
recommended dosages of, for cat, 904(t), 911(t)
for dog, 904(t), 911(t)
Doppler echocardiography, 135–138, 153, *155*. See also *Echocardiography.*
aortic regurgitation on, subaortic stenosis and, in dog, *490*
aortic stenosis on, 159
in dog, *136*, *490*
aortic valve blood flow velocity derived from, in cat, 154(t)
in dog, 154(t)
atrial septal defect on, in dog, *134*, *135*, *496*, Plates 7 & 8
atrioventricular valve dysplasia on, 158
in dog, *158*
blood flow monitoring via, in CPCR, 440
blood flow velocity derived from, 137
aliasing and, *137*, 139–140
intercept angle and, 136–137
Nyquist limit and, 139–140
valvular, in cat, 154(t)
in dog, 154(t)
cardiomyopathy on, 162, 163
chronic acquired valvular disease (endocardiosis) on, 161
color-flow, 139
applications of, 559, 574, Plate 3, Plates 5 to 10
continuous-wave. See *Continuous-wave Doppler echocardiography.*
diastolic function assessed via, 623
dilated cardiomyopathy on, 162
endocardiosis on, 161
evidence of endocarditis on, 574
hypertrophic cardiomyopathy on, 163
in cat, *627*, 633–634
imaging planes for, 143
indications for, 153–154
left-to-right shunt on, patent ductus arteriosus and, in dog, *156*

Doppler echocardiography *(Continued)*
ventricular septal defect and, in dog, *504*
left ventricular relaxation abnormality on, 624, *624*
mitral regurgitation on, in dog, *137*, Plate 10
mitral stenosis on, in cat, *136*
mitral valve blood flow velocity derived from, in cat, 154(t), *624*
in cat with cardiovascular abnormalities, *624*
in dog, 154(t)
myocardial diseases on, 162, 163
patent ductus arteriosus on, in dog, *156*
pseudonormalization on, 624, *624*
pulmonic stenosis on, 159–160
in dog, *136*, 160, *486*, Plate 3
pulmonic valve blood flow velocity derived from, in cat, 154(t)
in dog, 154(t)
pulsed-wave. See *Pulsed-wave Doppler echocardiography.*
restrictive filling pattern on, 624, *624*
shunt(ing) on, patent ductus arteriosus and, in dog, *156*
ventricular septal defect and, in dog, *504*
subaortic stenosis on, 159
in dog, *136*, *490*
Tetralogy of Fallot on, 160
tricuspid valve blood flow velocity derived from, in cat, 154(t)
in dog, 154(t)
tricuspid valve dysplasia on, 158
in dog, *158*
valvular blood flow velocities derived from, in cat, 154(t)
in dog, 154(t)
valvular disease on, chronic acquired, 161
valvular dysplasia on, 158
in dog, *158*
valvular regurgitation quantified via, 154
valvular stenosis on, 159–160
in cat, *136*
in dog, *136*, 160
ventricular septal defect on, in cat, Plate 5
in dog, *504*, Plate 6
Double-chambered right ventricle, 480
in dog, *481*
Double-outlet right ventricle, 519
Doxapram, adverse effects of, 911(t)
for respiratory arrest, 911(t)
recommended dosages of, for cat, 911(t)
for dog, 911(t)
Doxorubicin, as cardiotoxin, in cat, 657
in dog, 609
"Drop" (collapse), syncopal. See *Syncope.*
Drug(s), analgesic, for cat and dog, 854(t)
anesthetic. See also *Anesthesia.*
for cat and dog, 854(t), 858(t)
bioavailability of, dosage calculations based on, 310
cardiovascular. See also specific pharmaceutical classes and agents.
emergency use of, 431(t), 437–438
routes for, 435–437
recommended dosages of, for cat and dog, 903(t)–917(t)
side effects of, 908(t)–917(t)
and hypotension, in dog, 351, *351*
and syncope, 453
clearance and extraction of, 312
by liver, 312

Drug(s) *(Continued)*
half-life of, 213
preanesthetic, 858(t), 858–861, 859(t). See also *Anesthesia.*
sedative, for cat and dog, 854(t)
volume of distribution of, 312–313
Duchenne's cardiomyopathy, in dog, 607, *607*, 832
Ductus arteriosus, patent, 505–512
angiocardiographic findings associated with, 508–509
in dog, *508*
canine breed predisposition to, 460, 460(t)
coil occlusion of, 190
in dog, 511, *512*
echocardiographic evidence of, 154–155, 507
in dog, *156*, *510*
electrocardiographic findings associated with, 507
in dog, *510*
heart murmurs accompanying, 62
in dog, *62*
interventional cardiac catheterization for, 190
in dog, 511, *512*
left-to-right shunt accompanying, 507–508, 824
echocardiographic findings associated with, 154–155, 507
in dog, *156*, *510*
treatment of, in dog, 511, *512*
pathology of, 824
in dog, 824
prevalence of, in dog, 459(t), 459–460
pulmonary hypertension accompanying. See *Ductus arteriosus, patent, "reversed."*
"reversed," 509–512
echocardiographic findings associated with, 155, 510
right-to-left shunt accompanying, 509–512, 824
echocardiographic findings associated with, 155, 510
treatment of, 190, *876*, 876–877, *877*
in dog, 511, *512*
complications of, 511, *512*
in dog with heart failure, 228
recanalization following, 877
volume overload associated with, 209–210, *210*
Ductus venosus, patent, 529
Dysplasia, atrioventricular valve, 158
echocardiographic findings associated with, 158
in dog, *158*
pathology of, 824
mitral valve, 523–524, 525, 526
angiocardiographic findings associated with, 524
in dog, *189*, *525*
canine breed predisposition to, 462
electrocardiographic findings associated with, 523
in dog, *524*
prevalence of, in dog, 459(t), 462
radiographic findings associated with, 523
in dog, *523*
right ventricular, arrhythmogenic, in cat, 653–655, *654*, *655*, 831–832
in dog, 609
in man, 608–609
tricuspid valve, 158, 524–526

Dysplasia *(Continued)*
angiocardiographic findings associated with, 525
canine breed predisposition to, 461–462
echocardiographic findings associated with, 158
in dog, *158*
electrocardiographic findings associated with, 525
in dog, *524*
prevalence of, in dog, 459(t), 461–462
radiographic findings associated with, 525
in dog, *114, 523*
valvular, 158
echocardiographic findings associated with, 158
in dog, *158*
Dyspnea, 46
causes of, 43
signs accompanying, 46, *47*
Dystrophy, muscular, in dog, 606–607, 832
myocardial lesions associated with, 607, *607*

Early afterdepolarizations, 298, *299*
Early diastolic heart sounds, 55
Ebstein's anomaly, 158
Eccentric myocardial hypertrophy, volume overload and, 208, 757, 818
ECG. See *Electrocardiographic characteristics; Electrocardiography.*
Echocardiography, 130–168
acquired heart disease on, 160–168
aortic regurgitation on, subaortic stenosis and, 492
in dog, *490*
aortic stenosis on, 159, 488, *489,* 490
in dog, *136,* 159, *159, 490, 491, 492,* Plate 4
aortic valve blood flow velocity derived from, in cat, 154(t)
in dog, 154(t)
arteriovenous fistula on, 790, *791*
atrial septal defect on, 157–158, 498
in dog, *134, 135, 496*
atrioventricular valve disease on, chronic acquired. See *Echocardiography, endocardiosis on.*
atrioventricular valve dysplasia on, 158
in dog, *158*
blood flow velocity derived from. See *Doppler echocardiography, blood flow velocity derived from.*
canine. See *Dog(s), echocardiography in.*
cardiac tamponade on, 164
in dog, *165*
cardiac tumor on, 168
in cat, *694*
in dog, *166,* 693, *694*
cardiomyopathy on, 162, 163
in cat, 633–634, 648–649
in dog, 591–594, 605, 607
chemodectoma on, cardiac, in dog, *166, 694*
color-flow Doppler, 139
applications of, 559, 574, Plate 3, Plates 5 to 10
color M-mode, Plate 4
congenital heart disease on, 154–160, 475–476
constrictive pericarditis on, 698
contrast, 134, *134, 135*

Echocardiography *(Continued)*
atrial septal defect on, in dog, *134, 135*
shunt(ing) on, atrial septal defect and, in dog, *134, 135*
cor triatriatum on, in dog, *527*
diastolic function assessed via, 623
dilated cardiomyopathy on, 162
in cat, *648,* 648–649
in dog, 591–594, *593*
dirofilariasis-related changes on, 167
in cat, 731, *733*
in dog, 710, *711*
Doppler studies in. See *Doppler echocardiography.*
double-chambered right ventricle on, in dog, *481*
Duchenne's cardiomyopathy on, in dog, 607, *607*
Eisenmenger's physiology on, 519
endocardiosis and mitral regurgitation on. See *Echocardiography, mitral regurgitation on.*
endomyocardial scarring on, idiopathic, 163
evidence of endocarditis on, 163, 573–575, *574*
in dog, *164*
examination table for, 140, *140*
feline. See *Cat(s), echocardiography in.*
heart disease on, acquired, 160–168
congenital, 154–160, 475–476
heartworm-related changes on, 167
in cat, 731, *733*
in dog, 710, *711*
hemangiosarcoma on, right atrial, in dog, *166, 694*
hypertrophic cardiomyopathy on, 163
in cat, *626, 627, 629, 633,* 633–634
in dog, 605, *606*
idiopathic endomyocardial scarring on, 163
imaging planes for, *133,* 141–143, *141–144*
intrapericardial cyst on, in dog, *686*
left-to-right shunt on, patent ductus arteriosus and, 154–155, 507
in dog, *156, 510*
ventricular septal defect and, in dog, *504*
left ventricular outflow tract obstruction on, HCM and, in cat, *626, 627*
left ventricular relaxation abnormality on, 624, *624*
mitral regurgitation on, 161, 546–550
in cat, *627*
in dog, *137, 161,* Plate 10
mitral stenosis on, in cat, *136*
mitral valve blood flow velocity derived from, in cat, 154(t), *624*
in cat with cardiovascular abnormalities, *624*
in dog, 154(t)
M-mode. See *M-mode echocardiography.*
muscular dystrophy–related myocardial lesions on, in dog, 607, *607*
myocardial diseases on. See *Echocardiography, cardiomyopathy on.*
myocardial fibrosis on, aortic stenosis and, 488, *489*
normal findings on, in cat, 146(t)
in dog, *133,* 145(t)
ostium primum/ostium secundum–type atrial septal defect on. See *Echocardiography, atrial septal defect on.*
patent ductus arteriosus on, 154–155, 507, 510

Echocardiography *(Continued)*
in dog, *156, 510*
"reversed," 155, 510
pericardial cyst on, in dog, *686*
pericardial effusion on, 164, 167, 693
in dog, *165, 167, 691, 693*
pleural effusion on, 167
in cat, *165, 168*
in dog, *165, 693*
pseudonormalization on, 624, *624*
pulmonic regurgitation on, 559
pulmonic stenosis on, 159–160, 482–483
in dog, *136,* 159–160, *160, 486,* Plate 3
pulmonic valve blood flow velocity derived from, in cat, 154(t)
in dog, 154(t)
restrictive cardiomyopathy on, 163
in cat, *643,* 644
restrictive filling pattern on, 624, *624*
"reversed" patent ductus arteriosus on, 155, 510
right atrial hemangiosarcoma on, in dog, *166, 694*
right-to-left shunt on, 134
atrial septal defect and, in dog, *134*
patent ductus arteriosus and, 155, 510
right ventricle on, double-chambered, in dog, *481*
scarring on, endomyocardial, idiopathic, 163
shunt(ing) on, atrial septal defect and, in dog, *134, 135*
patent ductus arteriosus and, 154–155, 507, 510
in dog, *156, 510*
ventricular septal defect and, in dog, *504*
sinus venosus–type atrial septal defect on. See *Echocardiography, atrial septal defect on.*
spontaneous contrast ("smoke") on, 167, 636–637, 661
in cat with hypertrophic cardiomyopathy, *633*
subaortic stenosis on, 159, 488, *489,* 490
in dog, *136,* 159, *159, 490, 491, 492,* Plate 4
tetralogy of Fallot on, 160, 517
in dog, *516*
three-dimensional, 134
thyrotoxicosis-related heart lesions on, in cat, 783
transesophageal, 132, 134
tricuspid regurgitation on, 557–558
tricuspid valve blood flow velocity derived from, in cat, 154(t)
in dog, 154(t)
tricuspid valve dysplasia on, 158
in dog, *158*
two-dimensional. See *Two-dimensional echocardiography.*
valvular blood flow velocities derived from, in cat, 154(t)
in dog, 154(t)
valvular dysplasia on, 158
in dog, *158*
valvular regurgitation quantified via, 154
valvular stenosis on, 159–160
in cat, *136*
in dog, *136,* 159, *159,* 160, *160*
vegetative mass on, endocarditis and, 163
in dog, *164*
ventricular septal defect on, 156–157
in cat, Plate 5
in dog, *157, 501, 502, 504,* Plate 6
vs. radiography, in terms of diagnostic yield, 107

Ectopic atrial tachycardia, in dog, *341*, 341–342
treatment of, 350–351
Ectopic beats. See also *Extrasystoles*.
and abnormal heart sounds, 57
Ectopic junctional tachycardia (automatic junctional tachycardia), in dog, 346–347
Edema, chlorothiazide for, 909(t)
hydrochlorothiazide for, 912(t)
peripheral, causes of, 44, 47
pulmonary. See *Pulmonary edema*.
Edrophonium, adverse effects of, 911(t)
for arrhythmias, 911(t)
recommended dosages of, for cat, 911(t)
for dog, 911(t)
Edrophonium chloride, for supraventricular tachycardia, in dog, 349
evidence of effectiveness of, on ECG, *351*
Effusion, pericardial. See *Pericardial effusion*.
pleural, 126
echocardiographic findings associated with, 167
in cat, *165, 168*
in dog, *165, 693*
in surgical patient, 857
radiographic findings associated with, 126
in cat with dilated cardiomyopathy, *648*
Einthoven triangle, in electrocardiography, 74, *76*
Eisenmenger's physiology, 157, 518–519
pulmonary lesions associated with, 826
Ejection sounds, 54
EKG. See *Electrocardiographic characteristics; Electrocardiography*.
Electrical alternans, pericardial effusion and, 90, 691–692
in dog, *90, 691*
Electrocardiographic characteristics. See also *Electrocardiography*.
of aberrant conduction, 100–101, *101*
of aldosteronism (Conn's disease), 765, *765*
of antiarrhythmic drug effects, 311(t)
in dog, 361, *361*
in dog with atrial flutter or fibrillation, *353*
in dog with supraventricular tachycardia, *349, 350, 351*
of aortic stenosis, 490
in dog, *489*
of atrial extrasystoles, 94
in cat, 391, *391*
in dog, *94*
of atrial fibrillation, 95–96
in cat, 392, *392*
in dog, *95*, 343, *343, 344, 401*
of atrial flutter, 94–95
in cat, 391
in dog, *95*, 342, *342, 401*
of atrial septal defect, 498
in dog, *499*
of atrial standstill due to hyperkalemia, in dog, *89*
of atrial tachycardia, in cat, 391, *392*
of atrioventricular block, 81–84
in cat, 82, *83*, 394–395, *395, 401*
in dog, 82, *82, 83, 401*
of atrioventricular nodal re-entrant tachycardia, in dog, 345, *346*
of automatic (ectopic) junctional tachycardia, in dog, 347
Electrocardiographic characteristics *(Continued)*
of bradyarrhythmias, in cat, *401*
in dog, *401*
of bundle branch block, *84*, 84–85, *85*
of bypass tract–mediated macro-re-entrant tachycardia, in dog, 347
of cardiomegaly, 77–80, *78–80*
of cardiomyopathy, in cat, 630, 631(t), 643–644, 648
in dog, 590(t), 590–591, 605
of concealed conduction, 101, *101*
of congenital heart disease, 476
of constrictive pericarditis, 697
of dilated cardiomyopathy, in cat, 648
in dog, 590(t), 590–591
in dog with episodic weakness, *449*
in dog without overt signs of disease, 594–595, 595(t)
of ectopic atrial tachycardia, in dog, 341, *341*
of ectopic (automatic) junctional tachycardia, in dog, 347
of electrical alternans due to pericardial effusion, 90, 691–692
in dog, *90, 691*
of endocarditis, 575
of fascicular block, *85*, 85–86
of hypercalcemia, 768, *768*
of hyperkalemia, 89–90, *768*, 769
in dog, *89*
of hypertrophic cardiomyopathy, in cat, 630, 631(t)
in dog, 605
of hypocalcemia, *768*, 769
in thyroidectomized cat, *784*
of hypokalemia, *768*, 769
of infectious endocarditis, 575
of left atrial enlargement, 78, *78*
of left bundle branch block, 84, *84*
of left ventricular enlargement, 79–80, *80*
of mitral regurgitation, 545
of mitral valve dysplasia, 523
in dog, *524*
of myocardial infarction, 88–89, *89*
of pacemaker effects, in dog, *404, 407, 408, 411, 413, 419–422, 424*
of parasystole, 101–102
of patent ductus arteriosus, 507
in dog, *510*
of pericardial effusion, 90, 691–692
in dog, *90, 691*
of persistent atrial standstill, 81
in cat, 81, *81*
in dog, 81
in dog with hyperkalemia, *89*
of potassium deficit, *768*, 769
of potassium overload, 89–90, *768*, 769
in dog, *89*
of pulmonic regurgitation, 559
of pulmonic stenosis, 481
in dog, *482*
of re-entrant activation. See *Re-entrant* entries.
of restrictive cardiomyopathy, in cat, 631(t), 643–644
of right atrial enlargement, 77–78
of right bundle branch block, 84–85, *85*
of right ventricular enlargement, 78–79, *79*
of sick sinus syndrome, in dog, 93, *93, 401*
of sinoatrial block, 80, *81*
of sinus arrest, 92–93, *93*
of sinus arrhythmias, 92, *92*
of sinus bradycardia, 91
Electrocardiographic characteristics *(Continued)*
in anesthetized cat, *92*
of sinus nodal disturbances, in cat, 390
in dog, 338, 339
of sinus tachycardia, 91
in hyperthyroid cat, *90*
of subaortic stenosis, 490
in dog, *489*
of supraventricular tachyarrhythmias, 96
in cat, 391
in dog, *96*
vs. ventricular tachyarrhythmias, 333–334, *333–338*
of tetralogy of Fallot, 517
of thromboembolism, in cat, 661
of thyrotoxic heart disease, in cat, *83*, 90, *90*, 782–783, *783*, 783(t)
of tricuspid valve dysplasia, 525
in dog, *524*
of ventricular asystole, 99–100
of ventricular extrasystoles, 97–98
in cat, 396, *396*
in dog, *98*
of ventricular fibrillation, 99, *99*
of ventricular flutter, 99
of ventricular pre-excitation, 86–87
in cat, *393*, 394
in dog, *86*
of ventricular septal defect, 503
in dog, *504*
of ventricular tachyarrhythmias, 98–99
in cat, 98, 99, 396, *397*
in dog, 98, 99, *99*
vs. supraventricular tachyarrhythmias, 333–334, *333–338*
Electrocardiography, 67–103, *73*. See also *Electrocardiographic characteristics*.
ambulatory. See *Electrocardiography, Holter (24-hour)*.
arrhythmia detection via, 77(t), 90–100
in cat, 389–390
results of. See specific findings cited under *Cat(s), electrocardiography in*.
in dog, 331–332
results of. See specific findings cited under *Dog(s), electrocardiography in*.
arrhythmia plus syncope detection via, 448–449, *449*
combined with phonocardiography, 52, *52*
computed, 102
Einthoven triangle in, 74, *76*
F waves on. See *Fibrillation; Flutter*.
heart rate calculation via, 74
historical development of, 67
Holter (24-hour), 102, *102*
in detection of arrhythmias and syncope, 448, *449*
in detection of canine arrhythmias, 331–332. See also *Dog(s), electrocardiography in*.
in CPCR, 440
indications for, 72, 73(t)
intracavitary, 103, *103*
ladder diagrams in, 100, *100, 101*
leads for, 68, 68(t), *69*, 70, *75, 76*
limitations of, 73, 77
mean electrical axis in, 74, 76
normal results of, 75(t)
postoperative, results of, in thyroidectomized cat, *783, 784*
P wave on. See *P wave*.
QRS complex on. See *QRS complex*.

Electrocardiography *(Continued)*
Q-T interval on. See *Q-T interval.*
recording of results in, 68, *68*
signal-averaging, 103
S-T segment on. See *ST segment.*
surface, 71
transtelephonic, 102
T wave on. See *T wave.*
24-hour. See *Electrocardiography, Holter (24-hour).*
Electrocution, cardiac manifestations of, 774
Electronic stethoscopes, 52
Elevational resolution (azimuthal resolution), in ultrasonography, 131
Embolism. See also *Thromboembolism.*
aortic, distal, in cat, 658, *658, 660, 662*
sequelae of, 44, *660, 663*
prevalence of, in cat, 467
brachial artery, in cat, sequelae of, *660*
saddle. See *Embolism, aortic, distal.*
Embolization, and infarction, as sequelae of infectious endocarditis, 570, *571*
Embolization technique, in treatment of patent ductus arteriosus, 190
in dog, 511, *512*
Emergency management, of cardiopulmonary arrest, 427–441. See also *Cardiopulmonary cerebral resuscitation.*
of hypertension, 808
Enalapril, adverse effects of, 911(t)
for DCM and heart failure, in cat, 651
in dog, 597
for HCM, in cat, 635, 636, 640
for HCM and myocardial infarction, in cat, 635
for heart failure, 237(t), 241–242, 485(t), 911(t)
in cat with dilated cardiomyopathy, 651
in dog with dilated cardiomyopathy, 597
for hypertension, 805(t), 911(t)
for myocardial infarction, in cat with hypertrophic cardiomyopathy, 635
for pulmonary edema. See also *Enalapril, for heart failure.*
in cat with hypertrophic cardiomyopathy, 261
recommended dosages of, for cat, 903(t), 911(t)
for dog, 903(t), 911(t)
Endocardial cushion defects, pathology of, 825
Endocardial fibroelastosis, 466, 527–528, 652
in cat, 527, 652
Endocardial pacemaker, implantation of, 414–415, 416(t)–418(t)
Endocardiosis, 536–558, 888
canine breed predisposition to, 463, 463(t), 540, *541*. See also *King Charles spaniel, endocardiosis in.*
epidemiology of, 540, *554*
etiology of, 538–539
heart failure in, 888–892. See also *Heart failure, mitral regurgitation and.*
heart murmur accompanying, in dog, 540, *541*, 544–545
correlated with severity of associated heart failure, *544, 545*
mitral regurgitation associated with, 161, 536–555. See also *Mitral regurgitation.*
neurohormonal response associated with, in dog, 542, *543*
pathology of, 537–538, 828

Endocardiosis *(Continued)*
in dog, *539*
prognosis associated with, 553
in dog, *553*
radiographic features of, *113*
rupture of chordae tendineae as sequela of, 553–554
rupture of left atrium as sequela of, 554–555, *555*
signs of, 544–545
surgery for, 877
Endocarditis. See also *Myocarditis.*
infectious, 567–578
advancing age as risk factor for, in dog, *568*
antibiotics for, 576, 577(t)
prophylactic use of, 577–578
diagnosis of, 571–575
criteria for, 572(t)
echocardiographic findings associated with, 163, 573–575, *574*
in dog, *164*
epidemiology of, 567–568
organisms commonly associated with, 576(t)
pathogenesis of, 568–570
pathology of, 567–568, *569*
in dog, *569*
prevalence of, in cat, 567
in dog, 464, 567, *568*
prevention of, 577–578
sequelae of, 570–571, *571*, 573
therapy for, 576–577, 577(t)
valvular lesions in, *569*, 570
vegetative, 163, 567–568, *569*
echocardiographic appearance of, *164*, 573, *574*
in dog, *164*
thrombotic, nonbacterial, 568
Endocardium, 15. See also *Endocardial* entries and *Endocarditis.*
cardiac jelly separating myocardium from, 4
cushion defects of, pathology of, 825
fibroelastosis of, 466, 527–528, 652
in cat, 527, 652, 827
Endomyocardial fibrosis, in cat, 465, 831, *831*
Endomyocardial form, of RCM, in cat, 641, 642, 643, *643*. See also *Restrictive cardiomyopathy.*
Endomyocardial scarring, idiopathic, echocardiographic findings associated with, 163
Endomyocarditis. See also *Endocarditis* and *Myocarditis.*
in cat, 465, 832
Endotracheal drug delivery, in advanced life support, 435–436
Endotracheal intubation, in basic life support, 429
Enflurane, as anesthetic agent, 862
English bulldog. See also *Dog(s).*
echocardiography in, cardiac tumor on, *166*
English Cocker spaniel. See also *Dog(s).*
dilated cardiomyopathy in, *583*
M-mode echocardiography in, normal findings on, 145(t)
English Setter. See also *Dog(s).*
echocardiography in, evidence of endocarditis on, *164*
English sheepdog. See also *Dog(s).*
dilated cardiomyopathy in, 582(t), *583*
English springer spaniel. See also *Dog(s).*
atrioventricular myopathy in, pathology of, *837*

Enhancement, acoustic, 132
Enrofloxacin, for endocarditis, 577(t)
Eosinophil(s), pulmonary infiltration of, in dog with heartworm disease, 716
treatment of, 714, 716, 718
subendocardial infiltration of, in cat, 643
Ephedrine, for shock, 283, 283(t)
Epicardial pacemaker implantation, 415, 419(t)
Epicardium (visceral pericardium), 14, 15, 679, 680. See also *Pericardial* entries.
Epinephrine, emergency use of, 431(t), 437, 911(t)
for shock, 283, 283(t)
Episodic weakness, 446. See also *Syncope.*
canine DCM and, electrocardiographic findings associated with, *449*
differential diagnosis of, 447(t)
Equilibrium radionuclide angiocardiography, 195
in evaluation of ventricular function, 195–198, *197*, 197(t), *198*
Equipment, for cardiac catheterization, 174, 175, *176*, 177
for cardiac pacing, 406–411, *410*. See also *Pacemaker.*
for cardiopulmonary cerebral resuscitation, 429
Equivalent dipole theory, 71–72, *72*
Erythrocyte(s), increase in mass of, cardiac manifestations of, 772–773
substitutes for, in management of shock, 280
Esmolol, 322
adverse effects of, 322, 911(t)
electrocardiographic parameters affected by, 311(t)
for arrhythmias, 322, 911(t)
in cat, 398
in cat with dilated cardiomyopathy, 650
in dog, 315(t), 348
for DCM and arrhythmias, in cat, 650
for supraventricular tachycardia, in dog, 348
for ventricular tachycardia, in cat, 398
recommended dosages of, for cat, 903(t), 911(t)
for dog, 903(t), 904(t), 911(t)
Esophagus, anomalies compressing, 120, 528
ultrasonographic transducer in, 132
Etomidate, as anesthetic agent, 861
Examination table, for echocardiography, 140, *140*
Exercise intolerance, 46–47
conditions contributing to, 43(t), 44
Exercise testing, for syncope, in dog, 449
Exhaustion, myocardial, in response to volume overload, 209
External chest compressions, in basic life support, 433–434
factors limiting effectiveness of, 434(t)
External jugular vein, right-sided cardiac catheterization via, 177, *178*. See also *Cardiac catheterization.*
External pacemaker, 408. See also *Pacemaker.*
implantation of, 414(t)
Extracardiac stimulation, by pacemaker, 422
Extraction ratio, drug clearance and, 312
hepatic, 312
Extrasystoles. See also *Ectopic* entries.
atrial, 94
in cat, 391, *391*
in dog, *94*
junctional, 97

Extrasystoles *(Continued)*
in dog, *97*
ventricular, 97–98
in cat, 396, *396,* 397, 398
in dog, *98*
breed predisposition to, 466
with abnormal heart sounds, 57
Eye(s), effects of hypertension on, 802, 802(t), Plate 2
results of examination of, in diagnosis of cardiovascular disease, 45, 49, Plate 2

F waves, in dog with supraventricular tachycardia. See *Fibrillation, atrial, in dog; Flutter, atrial, in dog.*
Failing heart. See *Heart failure.*
Familial disorders. See *Genetic/familial basis.*
Far field, in ultrasonography, 131
Fascicular block, *85,* 85–86
Feline breed predisposition, to dilated cardiomyopathy, *623*
to hypertrophic cardiomyopathy, *623,* 624–625
Feline infectious peritonitis, pericardial lesions accompanying, *688*
Femoral artery, left-sided cardiac catheterization via, 179–180. See also *Cardiac catheterization.*
Femoral vein, right-sided cardiac catheterization via, 177. See also *Cardiac catheterization.*
Fetus, cardiac work overload in, effect of, 9–10
circulation in, 8, *8*
transition from, to blood flow in newborn animal, 8–9
myocardial cell growth in, 9
Fever, infectious endocarditis and, 572
Fibrillation, atrial, 94–95
in cat, 392, *392*
in dog, *95,* 343, *343, 344,* 345, *401*
and dilated cardiomyopathy, 588, 591
lethality of, *601*
occurring asymptomatically, among large breeds, 466
temporary, 354
treatment of, 352, 354
evidence of drug effectiveness in, on ECG, *353*
murmurs and altered heart sounds associated with, 57
ventricular, 99, *99*
bretylium for, 909(t)
countershock for, 438–439
Fibroelastosis, endocardial, 466, 527–528, 652
in cat, 527, 652, 827
Fibrosis, endomyocardial, in cat, 465, 831, *831*
myocardial, aortic stenosis and, 487–488
echocardiographic findings associated with, 488, *489*
heart failure and, 819, 821
pulmonary, radiographic findings associated with, 126
thrombogenicity of, 659
Fick equation, 184
First heart sound, 54
split, 54
First-degree atrioventricular block, 82–83
in cat, 82, 394, *395*
in dog, 82, *82,* 375
First-pass radionuclide angiocardiography, 194, *194*
in evaluation of shunts, *194,* 194–195, *195, 196*
in evaluation of ventricular function, 198–199
Fistula(s), arteriovenous, 790–791
cardiac manifestations of, 762, 790
diagnosis of, 790
echocardiography in, 790, *791*
Fixation, of heart, 848–849
Flecainide, adverse effects of, 911(t)
for arrhythmias, 911(t)
in dog, 350, 354
for atrial fibrillation, in dog, 354
for supraventricular tachycardia, in dog, 350
recommended dosages of, for dog, 911(t)
Fluid therapy, in management of shock, 270, 275–279
Flutter, atrial, 94–95
in cat, 391–392
in dog, *342,* 342–343, *401*
treatment of, 352
evidence of drug effectiveness in, on ECG, *353*
ventricular, 99
Foramen ovale, 17
Fossa ovalis, 17
Fourth aortic arch, right, persistent. See *Aortic arch(es), right, persistent.*
Fourth heart sound, 56
Fox terrier. See also *Dog(s).*
radiography in, signs of pulmonic stenosis on, *482*
Frank-Starling law, 29–30
Frequency, of sound waves, 131
Fungal myocarditis, in dog, 612
Furosemide, 236
adverse effects of, 912(t)
for DCM and heart failure, in cat, 649, 651
in dog, 596, 597
for HCM and heart failure, in cat, 637, 638, 641
for heart failure, 223, 235(t), 236, 485(t), 912(t)
in cat with dilated cardiomyopathy, 649, 651
in cat with hyperthyroidism, 786
in cat with hypertrophic cardiomyopathy, 637, 638, 641
in cat with mitral regurgitation, 551
in dog with dilated cardiomyopathy, 596, 597
in dog with mitral regurgitation, 551, 552
International Small Animal Cardiac Health Council recommendations regarding, 905(t)
for hypertension, 805(t)
for mitral regurgitation and heart failure, in cat, 551
in dog, 551, 552
for pulmonary edema, 259, 260(t). See also *Furosemide, for heart failure.*
for renal failure associated with shock, 286
recommended dosages of, for cat, 903(t), 912(t)
for dog, 903(t), 912(t)

Gallop rhythms, 56–57
Gastric dilatation-volvulus, cardiac manifestations of, 771
Gastrointestinal tract, diseases of, cardiac manifestations of, 770–772
effects of shock on, 286
embolization to, in infectious endocarditis, *571*
Gated equilibrium radionuclide angiocardiography, 195
in evaluation of ventricular function, 195–198, *197,* 197(t), *198*
Genetic/familial basis, for dilated cardiomyopathy, in dog, 585
in man, 585
for hypertrophic cardiomyopathy, in cat, 625, 637
in man, 625
Gentamicin, for endocarditis, 577(t)
German shepherd. See also *Dog(s).*
dilated cardiomyopathy in, 582(t)
echocardiography in, pericardial effusion on, *165*
radiography in, signs of pericardial/peritoneopericardial diaphragmatic hernia on, *684*
small heart on, *111*
sudden death of, ventricular arrhythmias and, 370, 836
Gianturco coil embolization, for patent ductus arteriosus, 190
in dog, 511, *512*
Globulin(s), elevated serum levels of, cardiac manifestations of, 772–773
Glomerulonephritis, infectious endocarditis and, 570
Glucose, in management of shock, 286
Glycogen storage disease, 768, 837
Glycopyrrolate, adverse effects of, 315(t), 912(t)
as preanesthetic agent, 858(t), 859(t)
electrocardiographic parameters affected by, 311(t)
for arrhythmias, 912(t)
in dog, 315(t)
for atrioventricular block, in cat, 396
for cardiovascular drug–induced hypotension, in dog, 351
recommended dosages of, for cat, 904(t), 912(t)
for dog, 904(t), 912(t)
Golden retriever. See also *Dog(s).*
cardiac tumor in, echocardiographic findings associated with, *166*
dilated cardiomyopathy in, *583*
M-mode echocardiography in, normal findings on, 145(t)
muscular dystrophy in, 607, 832
pulmonary hypervascularity in, radiographic appearance of, 122–123, *124*
Gordon setter. See also *Dog(s).*
occlusion of patent ductus arteriosus in, *512*
Granulomatosis, eosinophilic, in dog with heartworm disease, 716–718
lymphomatoid, in dog with heartworm disease, 718
Great Dane. See also *Dog(s).*
dilated cardiomyopathy in, 582(t), *583, 584*
pericardial effusion in, echocardiographic findings associated with, *165*
Great vessels. See *Heart, valve(s) of.*
Greyhound. See also *Dog(s).*
M-mode echocardiography in, normal findings on, 145(t)
Growth hormone (somatotropin), 766

Growth hormone (somatotropin) *(Continued)*
excess secretion of, 766
in cat, 656
cardiovascular abnormalities associated with, 656
Guide wires, selection of, for cardiac catheterization, 177

Half-life, of drugs, 213
Half-power distance, in ultrasonography, 131
Halothane, as anesthetic agent, 862
HCM. See *Hypertrophic cardiomyopathy.*
Head and neck, examination of, 47–50
Heart, 15–21
acquired disease of. See *Heart disease(s), acquired* and specific conditions.
anatomy of, 15–21
external, 16, *16, 17*
internal, *18*
angiography of. See *Angiocardiography.*
apex of, 15, 16
atrial septal defect in. See *Atrial septal defect.*
atria of. See *Atrium (atria).*
auscultation of, 52–53, *53.* See also *Heart murmurs; Heart sound(s).*
base of, 15, *19*
fibrous "skeleton" at, 15, *19*
catheterization of. See *Cardiac catheterization.*
computed tomography of, *199,* 199–200
conduction system of. See *Conduction* entries.
congenital disease of. See *Congenital heart disease.*
contraction and relaxation of, cycle of, 33–35, *34*
damage to, affecting action potentials, 293–295, *294, 295*
disorders of. See *Heart disease(s); Heart failure;* and specific conditions.
drug injection in, and cardiopulmonary cerebral resuscitation, 436
Ebstein's anomaly of, 158
electrophysiology of, 291–293
abnormal, and arrhythmias, 295–303, 296(t). See also *Arrhythmia(s).*
embryologic development of, 3–7
enlargement of. See *Cardiomegaly.*
failure of. See *Heart failure.*
fixation of, 848–849
Frank-Starling law of, 29–30
growth of, 9, *9*
histopathologic sectioning of, 848, *848*
impaired performance of, responses to, 759(t)
innervation of, 22–23
layers of. See *Endocardium; Epicardium; Myocardium.*
magnetic resonance imaging of, 200, *200*
massage of, in basic life support, 434–435
muscle of. See *Myocardium.*
necropsy of, 845–849
nuclear imaging of. See *Radionuclide angiocardiography.*
opening of, at necropsy, 846, *846, 849*
outer fibroserous membrane of. See *Pericardium.*
output of. See *Cardiac output.*
overload on, response to, 209–210
during fetal period, 9–10
during postnatal period, 10

Heart *(Continued)*
in form of myocardial hypertrophy, 208, 757–758, 818
physiology of, 25–36. See also *Heart, electrophysiology of.*
septation of, 4–6, *6*
shape and size of, on radiography, 110–117. See also *Cardiomegaly.*
surgery of. See *Surgery.*
tamponade of, 689–690
echocardiographic findings associated with, 164
in dog, *165*
pathophysiology of, *689,* 689–690, *690*
pericardial effusion and. See *Effusion, pericardial.*
pericardiocentesis for, 694–695
tumors of, 120, 168, 679, 698–699, 836
and pericardial effusion, 686, 695
in cat, 657, *657, 688,* 698–699
echocardiographic findings associated with, *694*
prevalence of, 467
in dog, 610, 686, *687, 688,* 698
computed tomographic appearance of, *199*
echocardiographic findings associated with, *166,* 693, *694*
prevalence of, 466
radiographic findings associated with, *692*
surgery for, 880
ultrasonography of. See *Echocardiography.*
valve(s) of, *19,* 20–21. See also specific valves, e.g., *Mitral valve.*
acquired disease of, 536–559. See also *Endocardiosis.*
in cat, 462, 463
in dog, 463(t), 463–464
blood flow in or across, Doppler-derived velocity of, in cat, 154(t)
in dog, 154(t)
regurgitant, quantification of, via Doppler echocardiography, 154
sites of. See *Aortic regurgitation; Mitral regurgitation;* etc.
congenital disease of, in cat, 462, 463
in dog, 459(t)–461(t), 460, 461, 462, 463, 463(t)
development of, 6, *6*
defective, 6
dysplasia of, 158
echocardiographic findings associated with, 158
in dog, *158*
sites of. See site-specific sub-entries under *Dysplasia.*
stenosis of, 158–159
echocardiographic findings associated with, 159–160
in cat, *136*
in dog, *136,* 159, *159,* 160, *160*
sites of. See *Aortic stenosis; Mitral stenosis; Pulmonic stenosis; Tricuspid stenosis.*
vegetations on, in IE, 567–568, *569.* See also *Infectious endocarditis.*
echocardiographic appearance of, *164,* 573, *574*
in dog, *164*
ventricles of. See *Left ventricle; Right ventricle; Ventricle(s) of heart.*
weight of, in relation to body weight, 847
in cat, 847(t)
in cat with cardiomyopathy, 847(t)
in dog, 847(t)

Heart *(Continued)*
work overload on. See *Heart, overload on.*
worms in. See *Heartworm disease.*
Heart block. See specific types, e.g., *Atrioventricular block.*
Heart disease(s). See also specific conditions.
acquired, 536–559, 828–839. See also *Endocardiosis.*
arrhythmias accompanying, in cat, 387–388
prevalence of, in cat, 462, 463
in dog, 463–465
aids to diagnosis of. See *Cardiovascular disease, diagnosis of.*
arrhythmias associated with. See *Arrhythmia(s).*
canine breed predisposition to, 459(t)–461(t), 460–463, 463(t), 582(t), 582–583
congenital. See *Congenital heart disease* and specific lesions.
drugs for. See *Cardiovascular drugs.*
feline breed predisposition to, 462, 463
infectious. See *Infectious endocarditis; Infectious myocarditis.*
lung diseases combined with, 126, 759–762
lung diseases differentiated from, 43(t)
lung field in, radiographic, 121–125
neoplastic. See *Heart, tumors of.*
neurogenic, 772
nutritional factors in, 739–752
parasitic. See *Heartworm disease.*
pathology of, 817–839
prevalence of, 457–467
in cat, 458, 458(t), 462–463, 465
in dog, 457–467, 459(t)
signs of, 42–64, 43(t), 47(t)
interpretation of, *42*
surgery for. See *Surgery.*
thyrotoxic, in cat, 782–789, 830. See also *Hyperthyroidism, in cat.*
arrhythmias associated with, 388
changes in presentation of, in recent decades, 785
electrocardiographic findings associated with, *83,* 90, *90,* 782–783, *783,* 783(t)
radiographic evidence of, 783, *784*
valvular. See under *Heart, valve(s) of* and see also specific conditions.
Heart failure, 205–245
abdominal ultrasonographic findings associated with, 153
in dog, *153*
anemia and, 790
aortic regurgitation and, treatment of, 228
aortic stenosis and, treatment of, 228
arrhythmias associated with, in cat with cardiomyopathy, 387, 387(t)
in dog, 224, 371
treatment of, 224–225
biochemical derangements and, 205–206, *206*
cachexia secondary to, 47, *48,* 744–745
causes of, 887–888
classification of, 216–217, 225
by International Small Animal Cardiac Health Council, 885
treatment in relation to, *226*
definitions of, 205, 884
diagnostic criteria for, 887
dilated cardiomyopathy and. See "heart failure" sub-entries under *Dilated cardiomyopathy.*

Heart failure *(Continued)*
dirofilariasis and, in dog, 897–898
drugs for, 223–224, 229–245. See also specific agents and pharamaceutical classes.
endocardiosis and, 888–892. See also *Heart failure, mitral regurgitation and.*
excessive left ventricular moderator bands and, in cat, 832
functional derangements and, *206*, 207
heartworm disease and, in dog, 897–898
hepatic congestion accompanying, 822
high-output, 781. See also *Cardiac output, high.*
hypertension and, treatment of, 228
hyperthyroidism and, 782, 786. See also *Heart disease(s), thyrotoxic.*
hypertrophic cardiomyopathy and, in cat, *258*, 628, 900
treatment of, 225, 637, 638, 641, 901
idiopathic, in cat, 631(t), 645–652. See also "in cat" sub-sub-entries under *Dilated cardiomyopathy.*
infectious endocarditis and, 576
International Small Animal Cardiac Health Council approach to, 883–901
left-sided, vs. right-sided heart failure, 222–223
low-output, 225
low-sodium diet in management of, 237, 551, 740–741
International Small Animal Cardiac Health Council recommendations regarding, 905(t)
management of. See *Heart failure, treatment of.*
mechanical derangements and, 206, *206*
mitral regurgitation and, 544
treatment of, 225–227, 551–553
myocardial pathology in, 209, 818–819
neonatal, endocardial fibroelastosis and, 827
neurohormonal response to, 214, *758*
oxygen therapy for, 223
in cat with dilated cardiomyopathy, 650
in cat with hypertrophic cardiomyopathy, 637–638
pacemaker-related, 422–423
patent ductus arteriosus and, treatment of, 228
pathology of, 817–822
pathophysiology of, 205–214
pericardial disease and, management of, 218
pharmacotherapy for, 223–224, 229–245, 485(t). See also specific drug classes and agents.
in-hospital, 260(t)
pulmonic stenosis and, treatment of, 228
radiographic findings associated with, 107
in cat, *258*
in dog, *256, 257*
refractory, 228
renal consequences of, 211–214, *212*
restrictive cardiomyopathy and, in cat, treatment of, 225
right-sided, vs. left-sided heart failure, 222–223
shock and, 286
sodium-restricted diet in management of, 237, 551
subaortic stenosis and, treatment of, 228
syncope associated with, 451
systemic effects of, *213*

Heart failure *(Continued)*
tachycardia and, in dog, 587
treatment of, 216–245
drugs used in, 223–224, 229–245. See also specific agents and pharmaceutical classes.
functional classification and, *226*
goals of, 217(t)
in-hospital, 260(t)
International Small Animal Cardiac Health Council recommendations on, 905(t)
low-sodium diet in, 237, 551, 740–741
oxygen supplementation in. See *Heart failure, oxygen therapy for.*
timing of, *226*
Heart murmurs, *56*, 58–62. See also *Heart sound(s).*
aortic regurgitation and, in dog, 61
aortic stenosis and, in dog, *60*, 60–61
atrial septal defect and, 61
continuous, 62
diastolic, 61–62
dilated cardiomyopathy and, in dog, 589
endocardiosis and, in dog, 540, *541*, 544–545
in dog with heart failure, *544, 545*
hypertrophic cardiomyopathy and, in cat, 628, 630, *630*
in dog, 604
infectious endocarditis and, 572–573
innocent, 58–59
mitral regurgitation and, 59–60
in dog, *59*, 60
mitral stenosis and, in dog, 61, *62*
patent ductus arteriosus and, 62
in dog, *62*
physiologic, 58–59
pulmonic regurgitation and, 559
in dog, 62
pulmonic stenosis and, 61
systolic, 58–61
tricuspid regurgitation and, 60, 557
ventricular septal defect and, 61
Heart rate, 27
blood pressure in relation to, 28, *28*
calculation of, from electrocardiogram, 74
duration of diastole and systole correlated with, *33*
effects of heart failure on, 214
impulses affecting, 27, *28*
monitoring of, in CPCR, 439
Heart sound(s), 53–58. See also *Heart murmurs.*
1st, 54
split, 54
2nd, 54–55
split, 55, *55*, 55(t)
3rd, 55–56
abnormal, in dog with dilated cardiomyopathy, *56*
4th, 56
classification of, 53–54
diastolic, early, 55
ejection, 54
gallop rhythm, 56–57
monitoring of, in CPCR, 439
systolic click, 54
variations in, with arrhythmias, 57–58
Heartworm disease, 702–721, 727–734
adulticide therapy for, in cat, 733
in dog, 710–713
ancillary drugs used in, 713–714
thromboembolism due to, 719
antibiotic prophylaxis against, in cat, 734

Heartworm disease *(Continued)*
in dog, 721
canine, 702–721
caval syndrome associated with, in dog, 718–719
surgery for, 879
classification of, in dog, 707, 707(t)
clinical aspects of, in cat, 728–729, 729(t)
in dog, 706–707, 709
cor pulmonale associated with, in dog, 715
diagnosis of, in cat, 729(t), 729–730
in dog, 707–708
diethylcarbamazine for, in dog, 720–721
differential diagnosis of, in cat, 732
echocardiographic findings associated with, 167
in cat, 731, *733*
in dog, 710, *711*
eosinophilia as sequela of, in dog, 716
treatment of, 714, 716, 718
epizootiology of, in dog, 702
feline, 727–734
granulomatosis secondary to, in dog, 716–718
heart failure associated with, in dog, 897–898
index of cardiac effort in presence of, *760*
ivermectin for, in cat, 734, 913(t)
in dog, 719–720, 721, 913(t)
melarsomine dihydrochloride for, in dog, 711–712, 714, 913(t)
microfilaricidal therapy for, in dog, 719–720
milbemycin oxime for, in cat, 734, 914(t)
in dog, 721, 914(t)
moxidectin for, in dog, 721
occult, in dog, 705–706
pathogenesis of, in dog, 703–706
pathology of, 835
in cat, 729
in dog, 703–705, *703–705*, 709
pathophysiology of, in cat, 728
prophylaxis against, in cat, 734
in dog, 720–721
radiographic findings associated with, in cat, 123, 731, *731*
in dog, *117*, 123, *125*, 709–710, *710, 717*, 717–718
surgery for, in dog, 714, 879
thiacetarsamide for, in cat, 733
in dog, 712, 713, 905(t), 917(t)
Heat stroke, cardiac manifestations of, 773
Hemangiosarcoma, right atrial, 880
echocardiographic findings associated with, *166*, 168, *694*
in dog, *166, 687, 694*, 880
surgery for, 880
Hematocysts, in tricuspid valve, prevalence of, in dog, 463–464
Hematologic diseases, cardiac manifestations of, 772–773
Hemodynamic monitoring, 181–184
in CPCR, 441
in management of shock, 266(t), 266–269, 280–282, *281*, 281(t)
results of, prognostic significance of, 267, 268, *268*
intraoperative, 863, 867
output measurements in, 183–186, *185*
pressure measurements in, 181–183, *182, 183*
results of, 207(t), 282(t)
acceptable to optimal range of, 282(t)
myocardial compensation indicated by, 207(t)

Hemodynamic monitoring *(Continued)*
prognostic significance of, in shock, 267, 268, *268*
tricuspid regurgitation indicated by, 557
Hemoglobin saturation, monitoring of, in CPCR, 440
Hemorrhage, gastrointestinal, shock and, 286
secondary to warfarin therapy, in cat, 665, *665*
Heparin, adverse effects of, 912(t)
for disseminated intravascular coagulopathy, 287
for thromboembolism, 912(t)
in cat, 664, 912(t)
in dog, 912(t)
as element of therapy for heartworm disease, 713, 715
recommended dosages of, for cat, 912(t)
for dog, 912(t)
Hepatic clearance and extraction, of drugs, 312
Hepatic congestion, heart failure and, 822
Hepatic diseases, cardiac manifestations of, 772
Hepatocellular failure, cardiac manifestations of, 772
Hepatomegaly, radiographic appearance of, 127
Hernia, diaphragmatic, pericardial/peritoneopericardial, 526, 682–684, *683*
abnormalities accompanying, 835
age distribution of, in cats, *683*
in dogs, *683*
cysts associated with, 684
radiographic findings associated with, 118, 526, 683–684
in dog, *684*
Hetastarch, 277, 278(t)
in management of shock, 277–278
High-output heart failure, 781. See also *Cardiac output, high.*
High-permeability pulmonary edema, 253–254
History, in diagnosis of cardiovascular disease, 41–45, 42(t)
Holter monitoring, 102, *102*. See also *Electrocardiography.*
for arrhythmias and syncope, 448, *449*
for canine arrhythmias, 331–332. See also *Dog(s), electrocardiography in.*
Hydralazine, adverse effects of, 912(t)
for heart failure, 224, 485(t), 912(t)
in dog with mitral regurgitation, 552
for hypertension, 912(t)
for mitral regurgitation and heart failure, in dog, 552
for pulmonary edema, 260, 260(t)
in dog with mitral regurgitation, 261
for shock, 283, 283(t)
recommended dosages of, for cat, 912(t)
for dog, 904(t), 912(t)
Hydrochlorothiazide, adverse effects of, 912(t)
for edema, 912(t)
for heart failure, 235(t), 237, 485(t)
in cat with hypertrophic cardiomyopathy, 641
for hypertension, 805(t), 912(t)
for pulmonary edema, 912(t)
recommended dosages of, for cat, 912(t)
for dog, 903(t), 912(t)
Hydrocodone, adverse effects of, 912(t)
cough-suppressant dosages of, 904(t), 912(t)
Hydrocodone *(Continued)*
for tussive syncope, in dog, 453
Hydroxyethyl starch, 277, 278(t)
in management of shock, 277–278
Hyperadrenocorticism (Cushing's syndrome), 764–765
Hyperaldosteronism (Conn's disease), 765
electrocardiographic findings in, 765, *765*
Hypercalcemia, 768–769
electrocardiographic characteristics of, 768, *768*
Hypercoagulability, secondary to shock, 287
Hyperechoic tissue, 132. See also *Echocardiography.*
Hypereosinophilic syndrome, in cat, 643
Hyperglobulinemia, cardiac manifestations of, 772–773
Hyperkalemia, 769
arrhythmias associated with, in cat, 388
electrocardiographic findings associated with, 89–90, *768*, 769
in dog, *89*
persistent atrial standstill accompanying, in dog, *89*
reperfusion syndrome and, in cat with ischemic limb, 666
Hyperkinetic conditions, and high cardiac output, 781
Hypermagnesemia, 770
Hypermetabolic conditions, and high cardiac output, 781
Hyperplasia, myocardial, during normal fetal and early neonatal growth, 9
Hypersensitivity, carotid sinus, and syncope, 452
Hypersomatotropism (acromegaly), 766
in cat, 656
cardiovascular abnormalities associated with, 656
Hypertension, 795–809
diagnostic workup for, 467–468, 800(t)
end-organ disease due to, 468, 801–802
signs of, 802(t), Plate 2
heart failure associated with, treatment of, 228
in cat, 468, 656–657, 797
pharmacotherapy for, 805(t)
in dog, 468, 797
pharmacotherapy for, 805(t)
left ventricular hypertrophy secondary to, 830
pathogenesis of, 800–801
pulmonary, patent ductus arteriosus and. See *Ductus arteriosus, patent, "reversed."*
treatment of, 804–808
diet in, 745, 805–806
drug therapy in, 805, 805(t), 806–808
emergency measures in, 808
omega-3 fatty acids in, 745
Hyperthyroidism, in cat, 781–789
antithyroid drugs for, 786–787, 913(t)
arrhythmias associated with, 90, *90*, 388
cardiac manifestations of. See *Heart disease(s), thyrotoxic, in cat.*
occult, 784–785
radioactive iodine therapy for, 789
recurrent, after thyroidectomy, 789
scintigraphic findings in, 785, *785*
surgery for, 787, *788*. See also *Thyroidectomy.*
complications of, 787–789
systemic signs of, 782, *782*
methimazole for, in cat, 913(t)
Hypertonic saline, in fluid therapy for shock, 277
Hypertrophic cardiomyopathy, 601–606, 624–641
angiocardiographic findings associated with, in cat, 630, *633*, *662*
arrhythmias associated with, in cat, *387*, 387(t), 626, 630, 631(t), 635–636
breed predisposition to, among cats, *623*, 624–625
cardiomegaly associated with, in cat, *114*, *115*, *258*, 630, *631*
in dog, 594, *605*
clinical manifestations of, in cat, 628, 630
diastolic dysfunction associated with, in man, 625
differential diagnosis of, in cat, 634
echocardiographic findings associated with, 163
in cat, *626*, *627*, *629*, *633*, 633–634
in dog, 605, *606*
electrocardiographic findings associated with, in cat, 630, 631(t)
in dog, 605
etiopathogenesis of, in cat, 625
in dog, 603
in man, 625
genetic/familial basis for, in cat, 625, 637
in man, 625
heart failure accompanying, in cat, *258*, 628, 900
treatment of, 225, 637, 638, 641, 901
heart sounds and murmurs associated with, in cat, 628, 630, *630*
in dog, 604
in cat, 624–641
in dog, 601–606
left ventricular outflow tract obstruction associated with, 604
in cat, 626, *626*, *627*
treatment of, 639
in dog, treatment of, 606
limb contracture secondary to, in cat, *663*
limb paralysis accompanying, in cat, 628, *660*
mid–left ventricular gradient accompanying, in cat, 627
mitral regurgitation accompanying, in cat, 627, *627*
myocardial infarction accompanying, in cat, 635, 837, *838*
myocardial ischemia accompanying, in cat, 625–626
natural history of, in cat, 634
pathology of, 829. See also *Hypertrophy, myocardial.*
in cat, 628, *629*, *631*, 634, *819*, *820*, 829, Plate 11
in dog, 602, *603*, 829
pathophysiology of, in cat, 625–628
in dog, 603–604
phonocardiographic findings associated with, in cat, *630*
physical findings associated with, in cat, 628, 630
in dog, 604
prevalence of, among cats, *623*, 624–625
prognosis associated with, in cat, 634
pulmonary edema accompanying, in cat, *258*, 628, 630, *632*
treatment of, 261, 637–638
radiographic findings associated with, in cat, *114*, *115*, *258*, 630, *631*, *632*
in dog, 604, *605*
right ventricular outflow tract obstruction associated with, in cat, 628

Hypertrophic cardiomyopathy *(Continued)*
spontaneous echocardiographic contrast ("smoke") associated with, in cat, *633*
syncope associated with, 451
in cat, 636
systolic dysfunction accompanying, 628
tachyarrhythmias accompanying. See *Hypertrophic cardiomyopathy, arrhythmias associated with.*
therapy for, 218
in cat, 635–641
in dog, 606
thromboembolism associated with, in cat, 658. See also *Thromboembolism.*
Hypertrophic osteopathy, infectious endocarditis and, 570
Hypertrophy, myocardial. See also *Hypertrophic cardiomyopathy; Hypertrophy, ventricular.*
concentric, pressure overload and, 208, 758, 818
eccentric, volume overload and, 208, 757, 818
normal postnatal growth and, 9
ventricular, *116*. See also *Hypertrophy, myocardial.*
in dog with pulmonic stenosis, *482*
secondary to hypertension, 830
secondary to thyrotoxicosis, 830
without dilation. See *Hypertrophic cardiomyopathy.*
Hyperviscosity syndromes, cardiac manifestations of, 772–773
Hypoadrenocorticism (Addison's disease), 763–764
Hypocalcemia, 769
electrocardiographic characteristics of, *768*, 769, *784*
in thyroidectomized cat, 788–789
electrocardiographic evidence of, *784*
Hypoechoic tissue, 132. See also *Echocardiography.*
Hypokalemia, 769–770
electrocardiographic findings associated with, *768*, 769
potassium chloride for, 915(t)
potassium gluconate for, 915(t)
Hypomagnesemia, 743–744, 770
Hyponatremia, 740
Hypoparathyroidism, following thyroidectomy, 788, 789
Hypotension, cardiovascular drug–induced, in dog, 351, *351*
syncope due to, 446
Hypothermia, cardiac manifestations of, 773–774
Hypothyroidism, 762–763
following thyroidectomy, 789
Hypovolemic shock, 273, 273(t). See also *Shock.*
Hypoxemic shock, 273, 273(t). See also *Shock.*

Ibutilide, for atrial fibrillation, 354
Idiopathic endomyocardial scarring, echocardiographic findings associated with, 163
Idiopathic myocardial failure, in cat, 631(t), 645–652. See also "in cat" sub-sub-entries under *Dilated cardiomyopathy.*
Idiopathic pericardial effusion, 685
treatment of, 695
IE. See *Infectious endocarditis.*
Imaging planes, for echocardiography, *133*, 141–143, *141–144*
Imipenem, for endocarditis, 576, 577(t)
Immersion fixation, of heart, 848
Immune-mediated disorders, and dilated cardiomyopathy, in dog, 587
in man, 587
cardiac manifestations of, 775–776
secondary to infectious endocarditis, 570
Immunodeficiency syndromes, cardiac manifestations of, 776
Immunodiagnostic testing, for heartworm disease, in cat, 730
in dog, 707–708, 715–716
Impedance, acoustic, 131
Implantation, of pacemaker, 414(t), 414–415, *415*, 416(t)–419(t)
Impulse conduction, abnormalities of, and arrhythmias, 299–303
intraventricular, in cat, 398
Impulse initiation, enhanced, in ectopic foci, and arrhythmias, *296*, 296–299
Indicator dilution, in identification of shunts, *186*, 186–187
in measurement of cardiac output, 184–186, *185*
Infarction, embolization and, as sequelae of infectious endocarditis, 570, *571*
myocardial, 837–839
electrocardiographic findings associated with, 88–89, *89*
in cat with hypertrophic cardiomyopathy, 635, 837, *838*
in dog, 610
pathology of, 837–839, *838*
thallium scan indicating, 199
renal, in cat with thromboembolism, *661*
Infection, disorders due to. See *Infectious* entries and *Septic shock.*
pacemaker, 423
vector of, for *Dirofilaria immitis*, 702. See also *Heartworm disease.*
Infectious endocarditis, 567–578. See also *Infectious myocarditis.*
advancing age as risk factor for, in dog, *568*
antibiotics for, 576, 577(t)
prophylactic use of, 577–578
diagnosis of, 571–575
criteria for, 572(t)
echocardiographic findings associated with, 163, 573–575, *574*
in dog, *164*
epidemiology of, 567–568
organisms commonly associated with, 576(t)
pathogenesis of, 568–570
pathology of, 567–568, *569*
in dog, *569*
prevalence of, in cat, 567
in dog, 464, 567, *568*
prevention of, 577–578
sequelae of, 570–571, *571*, 573
therapy for, 576–577, 577(t)
valvular lesions in, *569*, 570
vegetative, 163, 567–568, *569*
echocardiographic appearance of, *164*, 573, *574*
in dog, *164*
Infectious myocarditis, 832–833. See also *Infectious endocarditis.*
in cat, *833*
in dog, 465, 610–612, 832, *833*
Infectious pericardial effusion, 685
treatment of, 695
Infectious pericarditis, 835
Infectious peritonitis, feline, pericardial lesions accompanying, *688*
Infiltrative cardiomyopathy, 698. See also *Heart, tumors of.*
in cat, 657, *657, 688, 694*
in dog, 610
Inflammatory response, systemic, syndrome of, 274, 274(t), 275(t)
treatment of, 276(t)
Inflow occlusion and pulmonary arteriotomy, for pulmonic stenosis, 870–871, *871*
Inhalant anesthetic agents, 862
Inotropic drugs, positive. See also specific agents, e.g., *Digitalis preparations; Dobutamine; Dopamine.*
for heart failure, 224, 229(t), 229–235, 260(t)
in cat with dilated cardiomyopathy, 650
in dog with dilated cardiomyopathy, 596
for pulmonary edema, 260. See also *Positive inotropic drugs, for heart failure.*
for shock, 270, 282–283, 283(t)
for surgical patient, 856
recommended dosages of, for cat, 904(t)
for dog, 904(t)
Insulin, 767
insufficient secretion of, 767–768
Interatrial septum, 17
defect in. See *Atrial septal defect.*
formation of, 5, *6*
Intercept angle, and Doppler-derived blood flow velocity, 136–137
International Small Animal Cardiac Health Council, 883
approach of, to heart failure, 883–901
cardiovascular drug dosages recommended by, 903(t)–917(t)
Interventional cardiac catheterization, 866–867
for patent ductus arteriosus, 190
in dog, 511, *512*
for pulmonic stenosis, 190
Interventricular septum, 15, 20
defect in. See *Ventricular septal defect.*
formation of, 4–5, *6*
Intestine, embolization to, in infectious endocarditis, *571*
Intracardiac drug injection, in CPCR, 436
Intracavitary electrocardiography, 103, *103*
Intralingual drug injection, in CPCR, 436–437
Intraosseous drug delivery, in CPCR, 436
Intrapericardial cysts, 684–685, *685, 686*
Intrapericardial pressure-volume relationships, 680
in dog, *680*
in dog with constrictive pericarditis, *680*
in dog with pericardial effusion, *680*
Intravascular coagulopathy, disseminated, shock and, 287
Intravenous drug injection, in CPCR, 435
Intraventricular conduction defects, 84–86
in cat, 398
Intubation, in basic life support, 429
Iodine, radioactive, for hyperthyroidism, 789
Irish setter. See also *Dog(s).*
radiography in, VSD-related findings on, *503*
Irish wolfhound. See also *Dog(s).*
dilated cardiomyopathy in, 582(t), *583*

Irish wolfhound *(Continued)*
M-mode echocardiography in, normal findings on, 145(t)
Ischemia, myocardial, in cat with hypertrophic cardiomyopathy, 625–626
in dog, 610
thallium scan indicating, 199
Isoflurane, as anesthetic agent, 862
Isoproterenol, for atrioventricular block, in cat, 396
for cardiovascular drug–induced hypotension, in dog, 351
indications for, 913(t)
recommended dosages of, for cat, 904(t), 912(t)
for dog, 904(t), 912(t)
Isosorbide dinitrate, adverse effects of, 913(t)
for heart failure, 224, 237(t), 240, 913(t)
in dog with mitral regurgitation, 552
recommended dosages of, for cat, 913(t)
for dog, 913(t)
Isosorbide mononitrate, for heart failure, 237(t), 240
in dog with mitral regurgitation, 552
Ivermectin, for heartworm disease, in cat, 734, 913(t)
in dog, 719–720, 721, 913(t)

Jackson technique, of surgery for patent ductus arteriosus, 877, *877*
Jelly, cardiac, 4
Jugular vein(s), distention of, significance of, 47, *48*, 49, 50
examination of, 49
pulse pattern in, 49, *49*, 50
pacemaker implantation via, 416(t)–418(t)
right-sided cardiac catheterization via, 177, *178*. See also *Cardiac catheterization.*
Junctional arrhythmias, 97
in dog, *97*, 346–347

Ketamine, as preanesthetic agent, 858(t), 859(t), 860
Kidney(s), disease of, cardiomyopathy associated with, 770
infectious endocarditis and, 570, *571*
pericarditis associated with, 770
effects of heart failure on, 211–214, *212*
effects of hypertension on, 802, 802(t)
effects of shock on, 286
embolization to, in infectious endocarditis, *571*
failure of, as complication of thyroidectomy, 789
shock and, 286
infarction of, in cat with thromboembolism, *661*
King Charles spaniel. See also *Dog(s).*
endocardiosis in, *554*
heart murmur accompanying, 540, *541*
intensity of, and severity of associated heart failure, *544*, *545*
neurohormonal response associated with, *543*
prognosis associated with, *553*
Kussmaul's sign, constrictive pericarditis and, 696

Labrador retriever. See also *Dog(s).*
Labrador retriever *(Continued)*
bypass tract–mediated macro-re-entrant tachycardia in, 347, 355
dilated cardiomyopathy in, 582(t), *583*
Ladder diagrams, in electrocardiography, 100, *100*, *101*
Laminar blood flow, 137
Laplace's law, 32, 207–208
Lateral resolution, in ultrasonography, 131
Lateral thoracotomy, 868, *869*
emergency, in basic life support, 434–435
Leads, electrocardiographic, 68, 68(t), *69*, *70*, *75*, *76*
pacemaker, 409, *410*
problems with, 415, 417, 419, *420*, *421*
Left atrioventricular orifice, 17
Left atrioventricular valve. See *Mitral valve.*
Left atrium, 15, 17
blood stasis in, and risk of thrombosis, in cat, 659
and spontaneous echocardiographic contrast ("smoke"), 167, 636
enlargement of. See also *Cardiomegaly.*
electrocardiographic findings associated with, 78, *78*
radiographic appearance of, 113–116
opening of, at necropsy, 846
rupture of, endocardiosis and, 554–555, *555*
Left coronary artery, 21
Left cranial vena cava, persistent, 529
in dog, *529*
Left lung, 15
Left ventricle, 15, 20
enlargement of. See also *Cardiomegaly; Left ventricle, hypertrophy of.*
electrocardiographic findings associated with, 79–80, *80*
radiographic appearance of, 113
excessive moderator bands of, in cat, 465, 655–656, *656*, 827
and heart failure, 832
function of, radionuclide angiocardiography in evaluation of, 197(t)
hypertrophy of. See also *Myocardial hypertrophy.*
secondary to hypertension, 830
secondary to thyrotoxicosis, 830
without dilation. See *Hypertrophic cardiomyopathy.*
opening of, at necropsy, 846
outflow tract obstruction in, 822–823
hypertrophic cardiomyopathy and, 604
in cat, 626, *626*, *627*
in dog, treatment of, 606
relaxation of. See *Myocardial relaxation.*
wall stress–volume loop for, *219*
effects of myocardial failure on, *220*
Left-sided cardiac catheterization, 177, *178*, 179–180. See also *Cardiac catheterization.*
Left-sided heart failure. See also *Heart failure.*
vs. right-sided heart failure, 222–223
Left-to-right shunt, 824–825
as problem in surgical patient, 856–857
indicator dilution identifying, *186*
patent ductus arteriosus and, 507–508, 824
echocardiographic findings associated with, 154–155, 507
in dog, *156*, *510*
treatment of, in dog, 511, *512*
radionuclide angiocardiography in evaluation of, *194*, 194–195, *195*
ventricular septal defect and, echocardiographic findings associated with, in dog, *504*
Lhasa apso. See also *Dog(s).*
M-mode echocardiography in, endocardiosis on, *162*
Lidocaine, 317–318, 362–363
adverse effects of, 315(t), 318, 362, 913(t)
drugs interacting with, effects of, 326(t)
electrocardiographic parameters affected by, 311(t), 318
emergency use of, 431(t), 437
for arrhythmias, 317, 913(t)
in cat, 315(t), 398
in cat with dilated cardiomyopathy, 650
in dog, 315(t), 362–363
in dog with dilated cardiomyopathy, 597
for cardiopulmonary arrest, 431(t), 437
for DCM and arrhythmias, in cat, 650
in dog, 597
for ventricular tachycardia, in cat, 398
mechanism of action of, 362, *364*
recommended dosages of, for cat, 913(t)
for dog, 904(t), 913(t)
Life support. See also *Cardiopulmonary cerebral resuscitation.*
advanced, 435–437, *436*
basic, 429, 431–435, *432*
Ligamentum arteriosum, 21
Limb contracture, HCM-related thromboembolism and, in cat, *663*
Limb paralysis, amputation in management of, in cat, 665, *666*
dilated cardiomyopathy and, in cat, 647
hypertrophic cardiomyopathy and, in cat, 628, *660*
reperfusion following, complicated by hyperkalemia, in cat, 666
thromboembolism and, in cat, 44, 660, *660*
Liquor pericardii (pericardial fluid), 679–680
accumulation of excess of. See *Pericardial effusion.*
Lisinopril, adverse effects of, 913(t)
for HCM and myocardial infarction, in cat, 635
for heart failure, 237(t), 242, 913(t)
for hypertension, 805(t), 913(t)
for myocardial infarction, in cat with hypertrophic cardiomyopathy, 635
recommended dosages of, for cat, 913(t)
for dog, 913(t)
Liver, congestion of, heart failure and, 822
diseases of, cardiac manifestations of, 772
drug clearance and extraction by, 312
enlarged, radiographic appearance of, 127
Loop diuretics. See also specific agents, e.g., *Furosemide.*
for heart failure, 235(t), 236
Low-output heart failure, 225
Low-sodium diet, for cat, 741(t)
for dog, 741(t)
in management of heart failure, 237, 551, 740–741
International Small Animal Cardiac Health Council recommendations regarding, 905(t)
in management of hypertension, 745
Lung(s), 15. See also *Lung disease(s)* and *Pulmonary* entries.
alveolar-capillary structure of, 251, *252*
effects of injury to, 253–254. See also *Pulmonary edema.*
disorders of. See *Lung disease(s).*
edema of. See *Pulmonary edema.*

Lung(s) *(Continued)*
effects of shock on, 286–287
eosinophilic infiltration of, in dog with heartworm disease, 716
treatment of, 714, 716, 718
left, 15
right, 15
Lung disease(s). See also *Pulmonary* entries.
canine breed predisposition to, 43(t)
cardiac diseases combined with, 126, 759–762
cardiac diseases differentiated from, 43(t)
dirofilariasis and, in dog, 716–718
treatment of, 714, 716, 718
obstructive, chronic, 761
signs of, 43(t)
thromboembolic, 761–762
prevalence of, in dog, 467
vascular, prevalence of, in dog, 467
Lung field, in radiography, 121–125
Lung sounds, pulmonary edema and, 256
Lupus erythematosus, systemic, cardiac manifestations of, 775–776
Lyme disease, in dog, 612
and myocarditis, 612
Lymph, 21
Lymph nodes, 21, 22
Lymphadenopathy, appearance of, on radiography, 120, *121*
Lymphatics, pulmonary, 252
Lymphomatoid granulomatosis, in dog with heartworm disease, 718
Lymphosarcoma, in cat, 836
and infiltrative cardiomyopathy, *657, 688, 694*
in dog, and infiltrative cardiomyopathy, 610

Macrolide antibiotics, in management of shock, 285
in prophylaxis against heartworm disease, in cat, 734
in dog, 721
Macro-re-entrant tachycardia, bypass tract–mediated, in dog, 347, 355
Magnesium, dietary, as provided in commercial dog foods, 742(t)–743(t)
diminished serum levels of, 743–744, 770
elevated serum levels of, 770
Magnetic resonance imaging (MRI), of heart, 200, *200*
Malnutrition, cardiac manifestations of, 777
Mannitol, for renal failure associated with shock, 286
Massage, cardiac, in basic life support, 434–435
carotid sinus, 450
in differentiation of tachyarrhythmias, in dog, 335–336, *339*
in provocative testing for syncope, 450
Mean electrical axis, in electrocardiography, 74, 76
Median sternotomy, 867
Mediastinum, 14
radiography of, 120–121
Medical history, in diagnosis of cardiovascular disease, 41–45, 42(t)
Melarsomine dihydrochloride, for heartworm disease, in dog, 711–712, 714, 913(t)
Mesothelial cells, reactive, in pericardial effusion, *836*
Mesothelioma, pericardial, 695
Mesothelioma *(Continued)*
in dog, 686, *688*
Metabolic shock, 273(t), 273–274. See also *Shock.*
Metastatic infection, as complication of endocarditis, 570
Methimazole, for hyperthyroidism, 786–787
Methoxyflurane, as anesthetic agent, 862
Metoprolol, adverse effects of, 913(t)
for arrhythmias, 913(t)
in dog, 315(t)
in dog with dilated cardiomyopathy, 598
for heart failure, 243–244
for hypertension, 913(t)
for vasovagal syncope, 452
recommended dosages of, for cat, 913(t)
for dog, 913(t)
Metronidazole, for endocarditis, 577(t)
Mexiletine, 319
adverse effects of, 315(t), 319, 914(t)
electrocardiographic parameters affected by, 311(t)
for arrhythmias, 319, 914(t)
in dog, 315(t), 365–366
for ventricular tachycardia, in dog, 365–366
recommended dosages of, for dog, 904(t), 914(t)
Microfilariae testing, in cat, 728, 730
in dog, 708
Microfilaricidal therapy, in dog, 719–720
Mid–left ventricular gradient, in cat with hypertrophic cardiomyopathy, 627
Milbemycin oxime, for heartworm disease, in cat, 734, 914(t)
in dog, 721, 914(t)
Milrinone, for heart failure, 224, 229(t), 234–235
Miniature poodle. See also *Poodle; Dog(s).*
cardiac tumor in, echocardiographic findings associated with, *166*
M-mode echocardiography in, normal findings on, 145(t)
Miniature schnauzer. See also *Dog(s).*
sick sinus syndrome and tachycardia in, 355
sinoatrial block in, *81*
Mitral regurgitation, 220–222, 536–555
echocardiographic findings associated with, 161, 546–550
in cat with hypertrophic cardiomyopathy, *627*
in dog, *137, 161,* Plate 10
electrocardiographic findings associated with, 545
endocardiosis and, 161, 536–555. See also *Endocardiosis.*
heart failure associated with, 544
treatment of, 225–227, 551–553
heart murmur accompanying, 59–60
in dog, *59,* 60
hypertrophic cardiomyopathy and, in cat, 627, *627*
magnetic resonance imaging of, in dog, *200*
pathophysiology of, 540–543
pulmonary edema accompanying. See also *Mitral regurgitation, heart failure associated with.*
management of, 223–224
in dog, 261
radionuclide angiocardiographic findings associated with, in dog, *198*
surgery for, 877–878
treatment of, 550–553
Mitral stenosis, 823
echocardiographic findings associated with, in cat, *136*
heart murmur accompanying, in dog, 61, *62*
pathology of, 823
in cat, 823
in dog, 823
Mitral valve, 20, 537
blood flow in or across, Doppler-derived velocity of, in cat, 154(t), *624*
in cat with cardiovascular abnormalities, *624*
in dog, 154(t)
regurgitant. See *Mitral regurgitation.*
dysplasia of, 523–524, 525, 526
angiocardiographic findings associated with, 524
in dog, *189, 525*
canine breed predisposition to, 462
electrocardiographic findings associated with, 523
in dog, *524*
prevalence of, in dog, 459(t), 462
radiographic findings associated with, 523
in dog, *523*
stenosis of. See *Mitral stenosis.*
M-mode echocardiography, 132. See also *Echocardiography.*
advantages of, 132
aortic stenosis on, in dog, *491,* Plate 4
chronic acquired valvular disease (endocardiosis) on, in dog, *162*
color, Plate 4
dilated cardiomyopathy on, in dog, *593*
dirofilariasis-related changes on, in dog, *711*
disadvantages of, 132
endocardiosis on, in dog, *162*
evidence of endocarditis on, 574, *574*
heartworm-related changes on, in dog, *711*
hypertrophic cardiomyopathy on, in cat, *626, 627*
in dog, *606*
imaging planes for, *133,* 142
normal findings on, in cat, 146(t)
in dog, *133,* 145(t)
pericardial effusion on, in dog, *167, 691*
pleural effusion on, in cat, *168*
subaortic stenosis on, in dog, *491,* Plate 4
valvular disease on, chronic acquired, in dog, *162*
Mobitz-type atrioventricular block, 82–83
in cat, *83,* 395, *395*
Moderator bands, excessive, in left ventricle of cat, 465, 655–656, *656,* 827
as cause of heart failure, 832
Morphine, adverse effects of, 914(t)
as analgesic, for cat with ischemic limb, 666
as anxiolytic, for dog with pulmonary edema, 260, 260(t)
for pulmonary edema, 914(t)
recommended dosages of, for cat, 905(t), 914(t)
for dog, 905(t), 914(t)
Mosquito, as host to *Dirofilaria immitis,* 702. See also *Heartworm disease.*
Mouth-to-mouth ventilation, in basic life support, 431
Mouth-to-nose ventilation, in basic life support, 431
Moxalactam, for endocarditis, 577(t)
Moxidectin, for heartworm disease, in dog, 721

MRI (magnetic resonance imaging), of heart, 200, *200*
Mucosal sloughing, from gastrointestinal tract, secondary to shock, 286
Mucous membranes, changes in color of, significance of, 44–45, 47–49, Plate 1
monitoring of color of, in CPCR, 439
Multiple organ dysfunction syndrome, 274(t), 274–275, 275(t), 571. See also *Septic shock.*
treatment of, 276(t)
Murmurs. See *Heart murmurs.*
Muscular dystrophy, in dog, 606–607, 832
myocardial lesions associated with, 607, *607*
Mycotic myocarditis, in dog, 612
Myocardial cell death, in heart failure, 818–819
Myocardial compliance, 30, *31, 217,* 217–218
Myocardial contractility, 29. See also *Myocardium, force of contraction of.*
Myocardial depressant factor, 771
Myocardial diseases. See *Cardiomyopathy (cardiomyopathies).*
Myocardial exhaustion, in response to volume overload, 209
Myocardial failure. See *Heart failure.*
Myocardial fibrosis, aortic stenosis and, 487–488
echocardiographic findings associated with, 488, *489*
heart failure and, 819, 821
Myocardial form, of RCM, in cat, 641, 642, *642.* See also *Restrictive cardiomyopathy.*
Myocardial hyperfunction, in response to volume overload, 209
Myocardial hyperplasia, during normal fetal and early neonatal growth, 9
Myocardial hypertrophy. See also *Hypertrophic cardiomyopathy; Hypertrophy, ventricular.*
concentric, pressure overload and, 208, 758, 818
eccentric, volume overload and, 208, 757, 818
normal postnatal growth and, 9
Myocardial infarction, 837–839
electrocardiographic findings associated with, 88–89, *89*
in cat with hypertrophic cardiomyopathy, 635, 837, *838*
in dog, 610
pathology of, 837–839, *838*
thallium scan indicating, 199
Myocardial injury, from volume overload, 209
Myocardial ischemia, in cat with hypertrophic cardiomyopathy, 625–626
in dog, 610
thallium scan indicating, 199
Myocardial oxygen consumption, 33, 34
Myocardial perfusion, evaluation of, based on uptake of radioisotopes, 199
Myocardial relaxation, 217
abnormal, electrocardiographic findings associated with, 624, *624*
Myocardial stiffness, 30, *30,* 32
Myocarditis, 832–833. See also *Endocarditis.*
in cat, 657, *657, 820,* 832, *833*
in dog, 465, 610–612, *611,* 832, *833*
Myocardium, 15. See also *Myocardial* entries and *Myocarditis.*
apoptosis of, heart failure and, 818–819
cardiac jelly separating endocardium from, 4
Myocardium *(Continued)*
compensatory capacity of, 207(t)
compliance of, 30, *31, 217,* 217–218
contractility of, 29. See also *Myocardium, force of contraction of.*
diseases of. See *Cardiomyopathy (cardiomyopathies).*
exhaustion of, in response to volume overload, 209
failure of. See *Heart failure.*
fibrosis of, aortic stenosis and, 487–488
echocardiographic findings associated with, 488, *489*
heart failure and, 819, 821
force of contraction of, 28–29
dependency of, on preload, 29–30
growth of, during normal fetal and early neonatal development, 9
during normal postnatal development, 9
hyperfunction of, in response to volume overload, 209
hyperplasia of, during normal fetal and early neonatal growth, 9
hypertrophy of. See *Myocardial hypertrophy.*
infarction of. See *Myocardial infarction.*
infection/inflammation of. See *Myocarditis.*
injury to, from volume overload, 209
ischemia of, in cat with hypertrophic cardiomyopathy, 625–626
in dog, 610
thallium scan indicating, 199
necrosis of, 818
in cat, Plate 11
oxygen content of, 33, *33*
perfusion of, evaluation of, based on uptake of radioisotopes, 199
relaxation of, 217
abnormal, electrocardiographic findings associated with, 624, *624*
sarcomere function in, 29, *29*
stiffness of, 30, *30,* 32
ultrastructure of, *10,* 10–11, *11*
Myopathy. See also *Cardiomyopathy (cardiomyopathies).*
atrioventricular, 81, 836–837
in cat, 392, 658, 836
electrocardiographic characteristics of, 81, *81*
in dog, 403, 466, 607–608, *608,* 836, *837*
electrocardiographic characteristics of, 81
hyperkalemia and, *89*
Myxomatous degeneration, of atrioventricular valves. See *Endocardiosis.*

Nadolol, adverse effects of, 914(t)
for arrhythmias, 914(t)
in dog, 315(t)
for heart failure, 244
for hypertension, 914(t)
recommended dosages of, for cat, 914(t)
for dog, 914(t)
Nafcillin, for endocarditis, 577(t)
Narcotics, as preanesthetic agents, 858(t), 859(t), 860–861
cough-suppressant, 904(t), 909(t), 912(t)
Near field, in ultrasonography, 131
Near-syncope, 446. See also *Syncope.*
Neck and head, examination of, 47–50
Necropsy, of heart and great vessels, 845–849
Necrosis, 818(t)
myocardial, 818
in cat, Plate 12
Neospora caninum, infection by, 611–612
Nervous system, central, diseases of, cardiac manifestations of, 772
syncope due to, 447, 452–453
Neurocardiogenic syncope, 452
Neurogenic heart disease, 772
Neurogenic syncope, 447, 452–453
Neurohormonal responses, in endocardiosis, 542, *543*
in heart failure, 214, *758*
Neurologic impairment, as sign of cardiovascular disease, 45
Neuromuscular blocking drugs, for surgical patient, 862–863
Newborn, cardiac work overload in, effect of, 10
circulation in, transition from fetal blood flow to, 8–9
myocardial cell growth in, 9
ventricular growth in, 9, *9*
Newfoundland. See also *Dog(s).*
dilated cardiomyopathy in, *583*
electrocardiographic findings associated with, 590(t)
Nitrates. See also specific agents, e.g., *Nitroglycerin; Nitroprusside.*
for heart failure, 223–224, 237(t), 239–240
in dog with mitral regurgitation, 552
Nitroglycerin, adverse effects of, 914(t)
for heart failure, 224, 237(t), 239–240, 914(t)
in cat with dilated cardiomyopathy, 650
in cat with hypertrophic cardiomyopathy, 637
in dog with mitral regurgitation, 552
for pulmonary edema, 260, 260(t). See also *Nitroglycerin, for heart failure.*
recommended dosages of, for cat, 904(t), 914(t)
for dog, 904(t), 914(t)
Nitroprusside, adverse effects of, 914(t)
for heart failure, 223–224, 237(t)
in dog with dilated cardiomyopathy, 596
for pulmonary edema, 260, 260(t), 914(t). See also *Nitroprusside, for heart failure.*
in dog with dilated cardiomyopathy, 261
in dog with mitral regurgitation, 261
for shock, 283, 283(t)
recommended dosages of, for cat, 914(t)
for dog, 904(t), 914(t)
Nitrous oxide, as anesthetic agent, 862
Nonbacterial thrombotic endocarditis, 568
Noncardiogenic pulmonary edema, 254, *259.* See also *Pulmonary edema.*
treatment of, 262
Nonrestrictive ventricular septal defects, 157
Nonselective angiocardiography, 187. See also *Angiocardiography.*
Norepinephrine, for shock, 283, 283(t)
Norfloxacin, for endocarditis, 577(t)
Nuclear cardiology. See *Radionuclide angiocardiography.*
Nutritional deficiencies, cardiac manifestations of, 777
Nutritional support, in management of shock, 287

Nyquist limit, and Doppler-derived blood flow velocity, 139–140

Obesity, cardiac manifestations of, 776
Object resolution, in ultrasonography, 131
Obstructive pulmonary disease, chronic, 761
Obstructive shock, 273, 273(t). See also *Shock.*
Occult hyperthyroidism, 784–785
Ocular lesions, hypertension and, 802, 802(t), Plate 2
results of examination for, in diagnosis of cardiovascular disease, 45, 49, Plate 2
Omega-3 fatty acids, effects of, on blood pressure, 745
Open-chest cardiac massage, in basic life support, 434–435
Open-heart surgery, for aortic stenosis, 873
inadvisability of, in treatment of pulmonic stenosis, 872
Organ dysfunction, multiple, syndrome of, 274(t), 274–275, 275(t)
treatment of, 276(t)
Orthopnea, 46
Orton modification, of patch-graft surgery, for pulmonic stenosis, 872
Osteopathy, hypertrophic, infectious endocarditis and, 570
Ostium primum–type atrial septal defect, 495, 825
echocardiographic findings associated with, in dog, *496,* Plate 8
gross morphology of, 825
in cat, *495*
Ostium secundum–type atrial septal defect, 157, 495, 825
echocardiographic findings associated with, in dog, *134*
gross morphology of, 825
in cat, *495*
Overload, on heart, response to, 209–210
during fetal period, 9–10
during postnatal period, 10
in form of myocardial hypertrophy, 208, 757–758, 818
Oximetry, 183–184
in CPCR, 440
in monitoring of anesthetized patient, 864
Oxygen, consumption of, in shock, *268,* 269, 282
and oxygen debt, 269
myocardial, 33, 34
delivery of, in shock, *268,* 269, 282
monitoring of partial pressure of, in CPCR, 441
monitoring of transport of, in CPCR, 440
in management of shock, 267
Oxygen therapy, and basic life support, in CPCR, 431–432
for heart failure, 223
in cat with dilated cardiomyopathy, 650
in cat with hypertrophic cardiomyopathy, 637–638
for pulmonary edema, 258–259. See also *Oxygen therapy, for heart failure.*
Oxyglobin, as red blood cell substitute, 280
Oxymorphone, recommended dosages of, for cat, 905(t)
Oxyradicals, toxic, complicating shock, 287

P wave, 72, 74
P wave *(Continued)*
and QRS complex, in supraventricular vs. ventricular tachyarrhythmias, in dog, 333–334, *336, 337, 338*
Pacemaker, 400–424
bipolar, 409, *410*
coding of, 406, *407*
complications associated with, 412, 414, 415, 417, 419–424
in dog, *413, 419–422, 424*
electrocardiographic findings associated with, in dog, *404, 407, 408, 411, 413, 419–422, 424*
electrophysiologic characteristics of, 403–406, *404*
endocardial, implantation of, 414–415, 416(t)–418(t)
epicardial, implantation of, 415, 419(t)
external, 408
implantation of, 414(t)
hemodynamic characteristics of, 411–414, *412*
implantation of, 414(t), 414–415, *415,* 416(t)–419(t)
indications for, 400, 402–403
leads for, 409, *410*
problems with, 415, 417, 419, *420, 421*
permanent, 408–409
programming of, 411
problems with, 419
rheobase and chronaxy in, *404,* 405
right atrial, implantation of, 418(t)
strength-duration curve for, *404,* 404–405
temporary, 408
implantation of, 414(t)
unipolar, 409, *410*
ventricular, implantation of, 416(t)–417(t), 419(t)
Pacemaker syndrome, 423
Palpation, of neck, 50
Pancreas, inflammatory disease of, cardiac manifestations of, 770–771
insulin secretion by, 767
insufficient, 767–768
Pancreatitis, cardiac manifestations of, 770–771
Papillary muscles, 19
Paralysis, limb, amputation in management of, in cat, 665, *666*
dilated cardiomyopathy and, in cat, 647
hypertrophic cardiomyopathy and, in cat, 628, *660*
reperfusion following, complicated by hyperkalemia, in cat, 666
thromboembolism and, in cat, 44, 660, *660*
Parasitic infestation. See *Heartworm disease.*
Parasympathetic effects, of antiarrhythmics, 309(t)
Parasystole, 101–102, 303
Parathyroid glands, inadvertent resection of, during thyroidectomy, 788
Paresis. See *Paralysis.*
Parietal pericardium, 679, 680. See also *Pericardial* entries.
Partial pressure, carbon dioxide, monitoring of, in CPCR, 441
oxygen, monitoring of, in CPCR, 441
Patch-graft technique, of surgery for pulmonic stenosis, *871,* 871–872
Patent ductus arteriosus, 505–512
angiocardiographic findings associated with, 508–509
in cat, *189*
in dog, *508*
Patent ductus arteriosus *(Continued)*
canine breed predisposition to, 460, 460(t)
coil occlusion of, 190
in dog, 511, *512*
echocardiographic evidence of, 154–155, 507
in dog, *156, 510*
electrocardiographic findings associated with, 507
in dog, *510*
heart murmurs accompanying, 62
in dog, *62*
interventional cardiac catheterization for, 190
in dog, 511, *512*
left-to-right shunt accompanying, 507–508, 824
echocardiographic findings associated with, 154–155, 507
in dog, *156, 510*
treatment of, in dog, 511, *512*
pathology of, 824
in dog, 824
prevalence of, in dog, 459(t), 459–460
pulmonary hypertension accompanying. See *Patent ductus arteriosus, "reversed."*
"reversed," 509–512
echocardiographic findings associated with, 155, 510
right-to-left shunt accompanying, 509–512, 824
echocardiographic findings associated with, 155, 510
treatment of, 190, *876,* 876–877, *877*
in dog, 511, *512*
complications of, 511, *512*
in dog with heart failure, 228
recanalization following, 877
volume overload associated with, 209–210, *210*
Patent ductus venosus, 529
PDA. See *Patent ductus arteriosus.*
PDE (phosphodiesterase) III inhibitors, for heart failure, 224, 229(t), 234–235
Pembroke Welsh corgi. See also *Dog(s).*
M-mode echocardiography in, normal findings on, 145(t)
Penicillins, for endocarditis, 577(t)
for shock, 284(t), 284–285
Percutaneous approach, to right-sided cardiac catheterization, 174–175. See also *Cardiac catheterization.*
Percutaneous transtracheal oxygen insufflation, in basic life support, 429
Perfusion fixation, of heart, 848–849
Perfusion indices, monitoring of, in CPCR, 439, 440
in management of shock, 267
myocardial, based on uptake of radioisotopes, 199
Pericardial cavity, 14, 679
Pericardial effusion, 690–696
acute, 691
cardiac tamponade in relation to. See *Tamponade, cardiac.*
chronic, 691
clinical manifestations of, 690–691
cytologic evaluation of, 695
echocardiographic findings associated with, 164, 167, 693
in dog, *165, 167, 691, 693*
effect of, on pericardial pressure-volume relationships, in dog, *680*
electrical alternans accompanying, 90, 691–692

Pericardial effusion *(Continued)*
in dog, *90, 691*
electrocardiographic findings associated with, 90, 691–692
in dog, *90, 691*
etiology of, in cat, 686
in dog, 685–686
idiopathic, 685
treatment of, 695
infectious, 685
treatment of, 695
in surgical patient, 857
pathology of, 835
pericardiocentesis for, 694–695
physical findings associated with, 691
prevalence of, in cat, 466
in dog, 466
radiographic findings associated with, 692–693
in dog, 118, *118*
reactive mesothelial cells in, *836*
surgery for, 695
tumors causing, 686, 695
Pericardial fluid (liquor pericardii), 679–680
accumulation of excess of. See *Pericardial effusion.*
Pericardial/peritoneopericardial diaphragmatic hernia, 526, 682–684, *683*
abnormalities accompanying, 835
age distribution of, in cats, *683*
in dogs, *683*
cysts associated with, 684
radiographic findings associated with, 118, 526, 683–684
in dog, *684*
Pericardiectomy, 879–880
Pericardiocentesis, 867
for pericardial effusion or cardiac tamponade, 694–695
Pericarditis, 835–836
constrictive, 696–698
in dog, 696–698
hemodynamic effects of, *680,* 696, *697, 698*
infectious, 835
uremic, 770
Pericardium, 14, 679–681. See also *Pericardial* entries and *Pericarditis.*
absence of, 681
acquired diseases of, 685–696
anatomy of, 679–680
congenital diseases of, 681–685, 835. See also specific types, e.g., *Pericardial/peritoneopericardial diaphragmatic hernia.*
constrictive thickening of. See *Pericarditis, constrictive.*
cysts in, 684–685, *685, 686*
disease of, 681–698. See also *Pericardial* entries.
management of, 218
surgery in, 879–880
pathology of, 835–836
function of, 680–681
innervation of, 680
mesothelioma of, 695
in dog, 686, *688*
parietal, 679, 680
perforations in, congenital, *681,* 681–682
pressure-volume relationships in, 680
in dog, *680*
in dog with constrictive pericarditis, *680*
in dog with pericardial effusion, *680*
vascular supply of, 680
Pericardium *(Continued)*
visceral, 679, 680
Peripheral arterial catheterization, in CPCR, 441
in left-sided cardiac catheterization, 177, *178,* 179–180. See also *Cardiac catheterization.*
Peripheral cyanosis, 49
Peripheral edema, causes of, 44, 47
Peripheral perfusion, monitoring of, in CPCR, 439
Peritoneopericardial diaphragmatic hernia. See *Pericardial/peritoneopericardial diaphragmatic hernia.*
Peritonitis, infectious, feline, pericardial lesions accompanying, *688*
Permanent pacemaker, 408–409. See also *Pacemaker.*
Persistent atrial standstill (atrioventricular myopathy), 81, 836–837
in cat, 392, 658, 836
electrocardiographic characteristics of, 81, *81*
in dog, 403, 466, 607–608, *608,* 836, *837*
electrocardiographic characteristics of, 81
hyperkalemia and, *89*
Persistent left cranial vena cava, 529
in dog, *529*
Persistent right aortic arch, 528
in cat, *528*
in dog, breed predisposition to, 462
prevalence of, 459(t), 462
surgery for, 878
Pharmacotherapy. See *Drug(s).*
Phenothiazines, as preanesthetic agents, 859(t), 859–860
Phenylephrine, adverse effects of, 914(t)
for arrhythmias, 914(t)
for shock, 283, 283(t)
for supraventricular tachycardia, in dog, 349
recommended dosages of, for dog, 914(t)
Phenytoin, adverse effects of, 315(t), 915(t)
electrocardiographic parameters affected by, 311(t)
for arrhythmias, 915(t)
in dog, 315(t)
interaction of chloramphenicol with, effects of, 326(t)
recommended dosages of, for dog, 904(t), 915(t)
Pheochromocytoma, 765–766
Phonocardiography, 52, *52.* See also *Heart murmurs; Heart sound(s).*
HCM-related changes on, in cat, *630*
heart murmurs on, in dog, *59, 60, 62*
split second heart sound on, in dog, *55*
third heart sound on, in dog with dilated cardiomyopathy, *56*
Phosphodiesterase III inhibitors, for heart failure, 224, 229(t), 234–235
Physical examination, in diagnosis of cardiovascular disease, 46–64
Pinscher. See *Doberman pinscher.*
Plasma, in management of shock, 279
vs. other colloids, 278(t)
Pleura(e), 14
Pleural cavities, 14
Pleural effusion, 126
echocardiographic findings associated with, 167
in cat, *165, 168*
in dog, *165, 693*
in surgical patient, 857
Pleural effusion *(Continued)*
radiographic findings associated with, 126
in cat with dilated cardiomyopathy, *648*
Plexogenic pulmonary arteriopathy, Eisenmenger's physiology and, 826
Pneumonitis, eosinophilic, in dog with heartworm disease, 716
Pneumothorax, in surgical patient, 857
Polyarthritis, infectious endocarditis and, 570
Polycythemia, cardiac manifestations of, 772–773
Poodle. See also *Dog(s).*
echocardiography in, endocardiosis on, *161, 162*
miniature. See *Miniature poodle.*
radiography in, features of heart failure on, *256*
pulmonary edema on, *257*
Positioning, for radiography, 108
Positive chronotropic drugs. See specific agents, e.g., *Atropine; Glycopyrrolate; Isoproterenol.*
Positive inotropic drugs. See also specific agents, e.g., *Digitalis preparations; Dobutamine; Dopamine.*
for heart failure, 224, 229(t), 229–235, 260(t)
in cat with dilated cardiomyopathy, 650
in dog with dilated cardiomyopathy, 596
for pulmonary edema, 260. See also *Positive inotropic drugs, for heart failure.*
for shock, 270, 282–283, 283(t)
for surgical patient, 856
recommended dosages of, for cat, 904(t)
for dog, 904(t)
Positive pressure ventilation, in basic life support, 432–433
Posterior paresis. See also *Paralysis, limb.*
in cat with thromboembolism, 44
Potassium, in commercial dog foods, 742(t)–743(t)
Potassium balance, disturbances of. See *Potassium deficit; Potassium excess.*
Potassium chloride, for hypokalemia, 915(t)
Potassium deficit, 741–742, 769–770
electrocardiographic characteristics of, *768,* 769
supplements countering, 915(t)
Potassium excess, 769
arrhythmias associated with, in cat, 388
electrocardiographic characteristics of, 89–90, *768,* 769
in dog, *89*
persistent atrial standstill accompanying, in dog, *89*
reperfusion syndrome and, in cat with ischemic limb, 666
Potassium gluconate, for hypokalemia, 915(t)
Potassium-sparing diuretics. See also specific agents, e.g., *Spironolactone.*
for heart failure, 235(t), 237
Potts' anastomosis, inadvisability of, in surgery for tetralogy of Fallot, 875
Prazosin, 239
adverse effects of, 915(t)
for heart failure, 237(t), 239, 915(t)
in man, 552
for hypertension, 805(t), 915(t)
recommended dosages of, for dog, 904(t), 915(t)
Preanesthetic drugs, 858(t), 858–861, 859(t)

Prednisone. See also *Steroids.*
  for sequelae of heartworm disease, in dog, 714, 716, 718
Pregnancy, cardiac changes occurring during, 777
Preload, 24–25
  force of myocardial contraction in relation to, 29–30
Premature beats. See *Extrasystoles.*
Pressure overload, and concentric myocardial hypertrophy, 208, 758, 818
Presyncope, 446. See also *Syncope.*
Procainamide, 314, 316, 363
  adverse effects of, 315(t), 316, 915(t)
  electrocardiographic parameters affected by, 311(t), 316
  for arrhythmias, 314, 915(t)
    in cat, 315(t), 398
    in dog, 315(t), 350, 363, 364–365
    in dog with dilated cardiomyopathy, 598
  for supraventricular tachycardia, in dog, 350
  for ventricular tachycardia, in cat, 398
    in dog, 363, 364–365
  recommended dosages of, for cat, 915(t)
    for dog, 904(t), 915(t)
Programming, of pacemaker, 411
  problems with, 419
  rheobase and chronaxy in, *404*, 405
Propafenone, 319–320
  adverse effects of, 315(t), 319–320, 915(t)
  drugs interacting with, effects of, 326(t)
  electrocardiographic parameters affected by, 311(t)
  for arrhythmias, 319, 915(t)
    in dog, 315(t), 350, 354
      evidence of effectiveness of, on ECG, *351*
  for atrial fibrillation, in dog, 354
  for supraventricular tachycardia, in dog, 350
      evidence of effectiveness of, on ECG, *350*
  recommended dosages of, for dog, 915(t)
Propantheline, for sick sinus syndrome, 450
  for vasovagal syncope, 452
Propofol, as anesthetic agent, 861
Propranolol, 320–321
  adverse effects of, 315(t), 321, 915(t)
  drugs interacting with, effects of, 326(t)
  electrocardiographic parameters affected by, 311(t)
    in dog with atrial flutter, *353*
  for arrhythmias, 320, 915(t)
    in cat, 315(t), 398
    in cat with hypertrophic cardiomyopathy, 636
    in dog, 315(t), 348, 349
  for congenital heart disease, 485(t)
  for HCM and arrhythmias, in cat, 636
  for HCM and heart failure, in cat, 637
  for HCM and left ventricular outflow tract obstruction, in cat, 639
  for HCM and myocardial infarction, in cat, 635
  for heart failure, 243
    in cat with hypertrophic cardiomyopathy, 637
  for hypertension, 805(t), 915(t)
  for hyperthyroidism, 786, 787
  for left ventricular outflow tract obstruction, in cat with hypertrophic cardiomyopathy, 639
Propranolol *(Continued)*
  for myocardial infarction, in cat with hypertrophic cardiomyopathy, 635
  for supraventricular tachycardia, in dog, 348, 349
  for ventricular tachycardia, in cat, 398
  recommended dosages of, for cat, 903(t), 915(t)
    for dog, 903(t), 915(t)
Propylthiouracil, for hyperthyroidism, 786
Protozoal myocarditis, in dog, 611–612
Pseudonormalization, echocardiographic findings associated with, 624, *624*
Pseudotruncus arteriosus, *513*, *516*, 520
Psychoacoustic aspects, of auscultation, 51, *51*
Pulmonary arteriopathy, plexogenic, Eisenmenger's physiology and, 826
Pulmonary arteriotomy, inflow occlusion and, for pulmonic stenosis, 870–871, *871*
Pulmonary artery(ies), as site of heartworms. See *Heartworm disease.*
  banding of, in surgery for ventricular septal defects, 874, *874*
  catheterization of, in CPCR, 441
Pulmonary circulation, 251–252
Pulmonary edema, 251–262
  air bronchograms as sign of, *256*, *257*, *258*, *259*, *261*
  cardiogenic. See *Heart failure.*
  clinical manifestations of, 256
  diagnosis of, 256–258
  dilated cardiomyopathy and, in dog, *256*
    treatment of, 261–262
    treatment of, 223–224
  diuretics for, 909(t), 912(t)
  genesis of, *210*, 210–211, 252–254
    stages of, 254–256
  heart failure and. See *Heart failure.*
  high-permeability, 253–254
  hypertrophic cardiomyopathy and, in cat, *258*, 628, 630, *632*
    treatment of, 261, 637–638
  in surgical patient, 856
  lung sounds in relation to, 256
  mitral regurgitation and, treatment of, 223–224
    in dog, 261
  noncardiogenic, 254, *259*
    treatment of, 262
  oxygen therapy in management of, 258–259. See also *Heart failure, oxygen therapy for.*
  primary alveolar-capillary membrane injury and, 253–254
  radiographic findings associated with, 125–126, 257–258
    in cat, 258, *258*, 630, *632*
    in dog, *256*, *257*, 258, *259*, *261*
  ruptured chordae tendineae and, in dog, *261*
  seizure and, in dog, *259*
  sodium nitroprusside for. See *Nitroprusside, for pulmonary edema.*
  thyrotoxic heart failure and, management of, in cat, 786
  treatment of, 258–262, 260(t). See also *Heart failure, treatment of.*
    anxiety reduction in, 260, 260(t)
    diuretics in, 909(t), 912(t)
    morphine in, 914(t)
    sodium nitroprusside in. See *Nitroprusside, for pulmonary edema.*
Pulmonary fibrosis, radiographic findings associated with, 126
Pulmonary hypertension, patent ductus arteriosus and. See *Patent ductus arteriosus, "reversed."*
Pulmonary hypervascularity, radiographic appearance of, 122–123, *124*
Pulmonary lymphatics, 252
Pulmonary trunk, 15, 21
  enlarged radiographic appearance of, 119, *120*
Pulmonary valve. See *Pulmonic valve.*
Pulmonary veins, 15
  development of, 7
Pulmonic regurgitation, 558–559
  and heart murmur, 559
    in dog, 62
Pulmonic stenosis, 159, 478–485
  angiocardiographic findings associated with, 481–482
    in dog, *189*, *484*
  balloon dilation for, 190, 868
  canine breed predisposition to, 461, 461(t)
  echocardiographic evidence of, 159–160, 482–483
    in dog, *136*, 159–160, *160*, *486*, Plate 3
  electrocardiographic findings associated with, 481
    in dog, *482*
  gross morphology/pathology of, 823
    in cat, 823
    in dog, 478, *479*, 480, 823
  heart failure accompanying, treatment of, 228
  heart murmur associated with, 61
  interventional cardiac catheterization for, 190
  prevalence of, in dog, 459(t), 460–461
  radiographic findings associated with, 481
    in dog, *482*
  right ventricular hypertrophy accompanying, in dog, *482*
  surgery for, *869*, 869–872, *871*
Pulmonic valve, 21
  blood flow in or across, Doppler-derived velocity of, in cat, 154(t)
    in dog, 154(t)
  regurgitant. See *Pulmonic regurgitation.*
  stenosis of. See *Pulmonic stenosis.*
Pulse(s), arterial, 62–64, *63*
    abnormal, in infectious endocarditis, 573
    monitoring of, in CPCR, 440
  jugular venous, 49, *49*, 50
Pulse oximetry, in CPCR, 440
  in monitoring of anesthetized patient, 864
Pulsed-wave Doppler echocardiography, 138
  advantages of, 138
  disadvantages of, 138
  mitral regurgitation on, in dog, *137*
  patent ductus arteriosus on, in dog, *156*
  pulmonic stenosis on, in dog, *486*
Pulsus alternans, 63, *63*
Pulsus bigeminus, 63, *63*
Pulsus paradoxus, 63, *63*, 690

QRS complex, 72, 74
  morphology of, in supraventricular vs. ventricular tachyarrhythmias, in dog, 333, *333*, *334*, *335*
  P wave and, in supraventricular vs. ventricular tachyarrhythmias, in dog, 333–334, *336*, *337*, *338*

Q-T interval, 74
abnormal, *87*, 87–88
Quinidine, 313–314
adverse effects of, 314, 315(t), 915(t), 916(t)
drugs interacting with, effects of, 326(t)
electrocardiographic parameters affected by, 311(t), 313
for arrhythmias, 313, 915(t), 916(t)
in dog, 315(t), 350
for supraventricular tachycardia, in dog, 350
recommended dosages of, for dog, 904(t), 915(t), 916(t)

Radioactive iodine, for hyperthyroidism, 789
Radiography, 107–128
abdominal structures on, 127
aortic arch on, size of, 119–120
aortic stenosis evidenced on, 489
in dog, *491*
cardiac silhouette on, *108*, 111(t). See also *Radiography, cardiomegaly on.*
cardiac tumor–related changes on, 120
in dog, *692*
cardiomegaly on, 111–117, *112*
congenital heart disease and, 474–475
dilated cardiomyopathy and, in cat, *648*
in dog, *256*, 591, *591*, *592*
endocardiosis and, *113*
hypertrophic cardiomyopathy and, in cat, *114*, *115*, *258*, 630, *631*
in dog, 604, *605*
thromboembolism and, in cat, 661
tricuspid regurgitation and, 557
in dog, *114*
cardiomyopathic changes on, in cat, 630, *631*, *632*, 644, 648, *648*
in dog, 591, *591*, *592*, 604, *605*
caudal vena cava on, 120
congenital heart defects on, 127, 127(t), 474–475
constrictive pericarditis on, 697
DCM-related changes on, in cat, 648, *648*
in dog, *256*, 591, *591*, *592*
dirofilariasis-related changes on, in cat, 123, 731, *731*
in dog, *117*, 123, *125*, 709–710, *710*, *717*, 717–718
evidence of endocardiosis on, *113*
evidence of endocarditis on, 575
features of heart failure on, 107
in cat, *258*
in dog, *256*, *257*
focal pulmonary lesions on, heart disease and, 126
HCM-related changes on, in cat, *114*, *115*, *258*, 630, *631*, *632*
in dog, 604, *605*
heart size on, 111–117. See also *Radiography, cardiomegaly on.*
heartworm-related changes on, in cat, 123, 731, *731*
in dog, *117*, 123, *125*, 709–710, *710*, *717*, 717–718
hepatomegaly on, 127
intrapericardial cysts on, in dog, *686*
left atrial enlargement on, 113–116. See also *Radiography, cardiomegaly on.*
left ventricular enlargement on, 113. See also *Radiography, cardiomegaly on.*
lung field in, 121–125

Radiography *(Continued)*
lymphadenopathy on, 120, *121*
mediastinal structures on, 120–121
mitral valve dysplasia manifested on, in dog, *523*
pericardial cysts on, in dog, *686*
pericardial effusion–related changes on, 692–693
in dog, 118, *118*
pericardial/peritoneopericardial diaphragmatic hernia on, 118, 526, 683–684
in dog, *684*
pleural effusion on, 126
in cat, *648*
positioning for, 108
prominent pulmonary trunk on, 119, *120*
pulmonary edema on, 125–126, 257–258
in cat, 258, *258*, 630, *632*
in dog, *256*, *257*, 258, *259*, *261*
pulmonary fibrosis on, 126
pulmonary hypervascularity on, 122–123, *124*
RCM-related changes on, in cat, 644
right atrial enlargement on, 116. See also *Radiography, cardiomegaly on.*
right ventricular enlargement on, *116*, 116–117, *117*. See also *Radiography, cardiomegaly on.*
signs of pulmonic regurgitation on, 559
signs of pulmonic stenosis on, 481
in dog, *482*
signs of subaortic stenosis on, 489
in dog, *491*
signs of thromboembolism on, in cat, 644
small heart on, 111, *111*
technical aspects of, 108
thoracic conformation on, *109*, 110
thyrotoxicosis-related heart lesions on, in cat, 783, *784*
tracheal collapse on, 121, *122*
tricuspid valve dysplasia manifested on, 525
in dog, *114*, *523*
views used in, 108, 109, 110
vs. echocardiography, in terms of diagnostic yield, 107
VSD-related findings on, 503
in dog, *503*
Radionuclide angiocardiography, 194, *194*
in evaluation of shunts, *194*, 194–195, *195*, *196*
in evaluation of ventricular function, 195–199, *197*, 197(t), *198*
Radionuclide imaging, of thyroid gland, in diagnosis of hyperthyroidism, 785, *785*
Ramipril, adverse effects of, 916(t)
for heart failure, 916(t)
for hypertension, 805(t), 916(t)
recommended dosages of, for cat, 916(t)
for dog, 916(t)
RCM. See *Restrictive cardiomyopathy.*
Reactive mesothelial cells, in pericardial effusion, *836*
Recanalization, following surgery for patent ductus arteriosus, 877
Red blood cell(s), increase in mass of, cardiac manifestations of, 772–773
substitutes for, in management of shock, 280
Re-entrant activation, and arrhythmias, 102, 300–303, *301*
Re-entrant tachycardia, atrioventricular nodal, in dog, 345–346, *346*
bypass tract–mediated, in dog, 347

Re-entrant tachycardia *(Continued)*
sinus nodal, in dog, 339, 341
Reflex syncope, 452
Regurgitant blood flow, quantified via Doppler echocardiography, 154
sites of. See *Aortic regurgitation; Mitral regurgitation;* etc.
Relaxation, myocardial, 217
abnormal, echocardiographic findings associated with, 624, *624*
Renal pathology. See *Kidney(s).*
Renin-angiotensin system, 211, *241*
Reperfusion syndrome, hyperkalemia due to, in cat with ischemic limb, 666
Resistance, vascular, systemic, *32*, 33
Resolution, in ultrasonography, 131
Respiratory disease. See *Lung disease(s).*
Respiratory failure, doxapram for, 911(t)
shock and, 286–287
Restrictive cardiomyopathy, 641–645
echocardiographic findings associated with, 163
in cat, 641–645
angiocardiographic findings associated with, 644, *644*
arrhythmias associated with, 387(t)
clinical manifestations of, 643
differential diagnosis of, 644
echocardiographic findings associated with, *643*, 644
electrocardiographic findings associated with, 631(t), 643–644
endomyocardial form of, 641, 642, 643, *643*
etiopathogenesis of, 641–642
heart failure accompanying, treatment of, 225
myocardial form of, 641, 642, *642*
pathology of, *642*, 642–643, *643*, *821*
pathophysiology of, 642
physical findings associated with, 643
prevalence of, *623*
therapy for, 218, 645
thromboembolism associated with, 658. See also *Thromboembolism.*
in man, 641
Restrictive filling pattern, echocardiographic findings associated with, 624, *624*
transition between impaired relaxation and, 624, *624*
Restrictive ventricular septal defects, 157
Resuscitation. See *Cardiopulmonary cerebral resuscitation.*
Retriever. See specific types, e.g., *Golden retriever; Labrador retriever.*
"Reversed" patent ductus arteriosus, 509–512
echocardiographic findings associated with, 155, 510
Reynold's number, for blood flow, 137
Rheobase, in programming of pacemaker, *404*, 405
Right aortic arch, persistent, 528
in cat, *528*
in dog, breed predisposition to, 462
prevalence of, 459(t), 462
surgery for, 878
Right atrial pacemaker, implantation of, 418(t)
Right atrioventricular orifice, 17
Right atrioventricular valve. See *Tricuspid valve.*
Right atrium, 15, 16–17
enlargement of. See also *Cardiomegaly.*
electrocardiographic findings associated with, 77–78, *78*

Right atrium *(Continued)*
radiographic appearance of, 116
hemangiosarcoma of, 880
echocardiographic findings associated with, *166*, 168, *694*
in dog, *166*, *687*, *694*, 880
surgery for, 880
opening of, at necropsy, 846
Right coronary artery, 21
Right costocervical vein, *418*
pacemaker implantation via, 415, 417(t)
Right lung, 15
Right ventricle, 15, 17, 19–20
double-chambered, 480
angiocardiographic findings associated with, in dog, *481*
echocardiographic findings associated with, in dog, *481*
double-outlet, 519
dysplasia of, arrhythmogenic. See *Right ventricular cardiomyopathy.*
enlargement of. See also *Cardiomegaly; Right ventricle, hypertrophy of.*
electrocardiographic findings associated with, 78–79, *79*
radiographic appearance of, *116*, 116–117, *117*
function of, radionuclide angiocardiography in evaluation of, 197(t)
hypertrophy of, *116*. See also *Myocardial hypertrophy.*
electrocardiographic findings associated with, in dog with pulmonic stenosis, *482*
opening of, at necropsy, 846
outflow tract obstruction in, hypertrophic cardiomyopathy and, in cat, 628
Right ventricular cardiomyopathy, in cat, 653–655, *654*, *655*, 831–832
in dog, 609
in man, 608–609
Right-sided cardiac catheterization, 177, *178*. See also *Cardiac catheterization.*
percutaneous (Seldinger) approach to, 174–175
Right-sided heart failure. See also *Heart failure.*
vs. left-sided heart failure, 222–223
Right-to-left shunt, 825–826
as problem in surgical patient, 856–857
atrial septal defect and, echocardiographic findings associated with, in dog, *134*
echocardiographic demonstration of, 134
in dog, *134*
indicator dilution identifying, *186*
patent ductus arteriosus and, 509–512, 824
echocardiographic findings associated with, 155, 510
radionuclide angiocardiography in evaluation of, 195, *196*
Rottweiler. See also *Dog(s).*
hypertrophic cardiomyopathy in, pathology of, *603*
Rupture, of chordae tendineae, 553
and pulmonary edema, in dog, *261*
in association with endocardiosis, 553–554
of left atrium, in association with endocardiosis, 554–555, *555*

"Saddle" embolism. See *Embolism, aortic, distal.*
Saline, hypertonic, in fluid therapy for shock, 277
Salt-restricted diet. See *Sodium-restricted diet.*
Saluki. See also *Dog(s).*
pacemaker for, electrocardiographic findings associated with, *404*
Sarcomere, 29, *29*
Scarring, endomyocardial, idiopathic, echocardiographic findings associated with, 163
Scattered echoes, 131
Schnauzer, miniature. See also *Dog(s).*
sick sinus syndrome and tachycardia in, 355
sinoatrial block in, *81*
Scintigraphy. See *Radionuclide* entries.
Scottish deerhound. See also *Dog(s).*
dilated cardiomyopathy in, *583*
Second-degree atrioventricular block, 82–83
in cat, *83*, 394–395, *395*, *401*
in dog, *82*, 375, *401*
Second heart sound, 54–55
split, 55, *55*, 55(t)
Sedatives, for cat, 854(t)
for dog, 854(t)
Seizure(s), 448
pulmonary edema secondary to, in dog, *259*
vs. syncope, 447–448
Seldinger technique, of cardiac catheterization, 174–175. See also *Cardiac catheterization.*
Selective angiocardiography, 187–188. See also *Angiocardiography.*
Sepsis syndrome, 570–571
Septation, of heart, 4–6, *6*
Septic shock, 273(t), 274–275, 571
cardiac manifestations of, 774–775
drug therapy for, 283(t), 284(t), 284–285
infectious endocarditis and, 571, 577
pathogenesis of, in man, *775*
Seroma, in pacemaker recipient, 424
Setter. See also *Dog(s).*
echocardiography in, evidence of endocarditis on, *164*
occlusion of patent ductus arteriosus in, *512*
radiography in, VSD-related findings on, *503*
Sevoflurane, as anesthetic agent, 862
Shadowing, acoustic, 132
Sheepdog, English. See also *Dog(s).*
dilated cardiomyopathy in, 582(t), *583*
Shih-tzu. See also *Dog(s).*
radiography in, right ventricular enlargement on, *117*
Shock, 265–287
cardiogenic, 272–273, 273(t)
classification of, 272–274, 273(t)
distributive, 273, 273(t)
hypovolemic, 273, 273(t)
hypoxemic, 273, 273(t)
management of, 270–271, 275–286
drug therapy in, 270–271, 282–286, 283(t), 284(t)
goals of, 269–270
hemodynamic monitoring in, 266(t), 266–269, 280–282, *281*, 281(t)
results of, prognostic significance of, 267, *268*, 269
obstructive, 273, 273(t)
organ-specific effects of, 286–287
oxygen consumption in, *268*, 269, 282
and oxygen debt, 269
oxygen delivery in, *268*, 269, 282
oxygen transport in, monitoring of, 267
Shock *(Continued)*
pathophysiology of, temporal aspects of, 266
prognostic factors in, 267, *268*, 269
septic, 273(t), 274–275, 571
cardiac manifestations of, 774–775
drug therapy for, 283(t), 284(t), 284–285
infectious endocarditis and, 571, 577
pathogenesis of, in man, *775*
Shunt(ing), 824–826
atrial septal defect and, 157, 496–497
echocardiographic findings associated with, in dog, *134*, *135*
bidirectional, ASD and, echocardiographic findings associated with, in dog, *135*
indicator dilution identifying, *186*, 186–187
left-to-right, 824–825
as problem in surgical patient, 856
indicator dilution identifying, *186*
patent ductus arteriosus and, 507–508, 824
echocardiographic findings associated with, 154–155, 507
in dog, *156*, *510*
treatment of, in dog, 511, *512*
radionuclide angiocardiography in evaluation of, *194*, 194–195, *195*
ventricular septal defect and, echocardiographic findings associated with, in dog, *504*
patent ductus arteriosus and, 507–512, 824
echocardiographic findings associated with, 154–155, 507, 510
in dog, *156*, *510*
treatment of, in dog, 511, *512*
radionuclide angiocardiography in evaluation of, *194*, 194–195, *195*, *196*
right-to-left, 825–826
as problem in surgical patient, 856–857
atrial septal defect and, echocardiographic findings associated with, in dog, *134*
echocardiographic demonstration of, 134
in dog, *134*
indicator dilution identifying, *186*
patent ductus arteriosus and, 509–512, 824
echocardiographic findings associated with, 155, 510
radionuclide angiocardiography in evaluation of, 195, *196*
ventricular septal defect and, 157
echocardiographic findings associated with, in dog, *504*
indicator dilution identifying, *186*
Siamese cat. See also *Cat(s).*
persistent atrial standstill in, electrocardiographic characteristics of, *81*
Siberian husky. See also *Dog(s).*
radiography in, pulmonary edema on, *259*
seizures in, pulmonary edema secondary to, *259*
Sick sinus syndrome, in dog, 93, *93*, 402–403
breed predisposition to, 355, 466
electrocardiographic findings associated with, 93, *93*, *401*
syncope accompanying, 450
tachycardia associated with, 355
Signal-averaging electrocardiography, 103

Signalment, in hyperthyroidism, 782, *782*
Silent atria. See *Persistent atrial standstill (atrioventricular myopathy).*
Sinoatrial block, 80, *81*
Sinoatrial node, 22
Sinus arrest, 92–93
Sinus arrhythmia, 92, *92*
Sinus bradycardia, 91
in cat, 390
surgical anesthetic complications and, *92*
Sinus nodal disturbances, in cat, 390
Sinus nodal re-entrant tachycardia, in dog, 339, 341
Sinus tachycardia, 91
in cat, 390
hyperthyroidism and, 90, *90*
in dog, 338–339
Sinus venosus–type atrial septal defect, 157, 495, 825
echocardiographic findings associated with, in dog, *135*, Plate 7
Skin/mucous membranes, changes in color of, significance of, 44–45, 47–49, Plate 1
monitoring of color of, in CPCR, 439
Small intestine, embolization to, in infectious endocarditis, *571*
"Smoke" (spontaneous echocardiographic contrast), 167, 636–637, 661
hypertrophic cardiomyopathy and, in cat, *633*
Sodium, dietary. See also *Sodium-restricted diet.*
as provided in commercial dog foods, 742(t)–743(t)
Sodium bicarbonate, use of, in CPCR, 431(t), 438
in management of shock, 286
Sodium ipodate, for hyperthyroidism, 787
Sodium nitroprusside, adverse effects of, 914(t)
for heart failure, 223–224, 237(t)
in dog with dilated cardiomyopathy, 596
for pulmonary edema, 260, 260(t), 914(t). See also *Sodium nitroprusside, for heart failure.*
in dog with dilated cardiomyopathy, 261
in dog with mitral regurgitation, 261
for shock, 283, 283(t)
recommended dosages of, for cat, 914(t)
for dog, 904(t), 914(t)
Sodium-restricted diet, for cat, 741(t)
for dog, 741(t)
in management of heart failure, 237, 551, 740–741
International Small Animal Cardiac Health Council recommendations regarding, 905(t)
in management of hypertension, 745, 805–806
Somatotropin (growth hormone), 766
excess secretion of, 766
in cat, 656
cardiovascular abnormalities associated with, 656
Sonography, 130–132
abdominal, signs of heart failure on, 153
in dog, *153*
cardiac. See *Echocardiography.*
transducer in, 131, 140
esophageal placement of, 132
Sonolucent tissue, 132. See also *Echocardiography.*
Sotalol, 323–324
adverse effects of, 315(t), 324, 916(t)
on dog, 367
drugs interacting with, effects of, 326(t)
electrocardiographic parameters affected by, 311(t)
for arrhythmias, 323–324, 916(t)
in dog, 315(t), 350, 354, 364, 366
in dog with dilated cardiomyopathy, 598
for atrial fibrillation, in dog, 354
for DCM and arrhythmias, in dog, 598
for supraventricular tachycardia, in dog, 350
for ventricular tachycardia, in dog, 364, 366
recommended dosages of, for cat, 916(t)
for dog, 916(t)
Spaniel. See specific types, e.g., *Cocker spaniel; King Charles spaniel.*
Specular echoes, 131
Spironolactone, 237
adverse effects of, 916(t)
for heart failure, 235(t), 237, 485(t), 916(t)
in cat with hypertrophic cardiomyopathy, 641
for hypertension, 805(t)
recommended dosages of, for cat, 916(t)
for dog, 903(t), 916(t)
Splitting, of first heart sound, 54
of second heart sound, 55, *55*, 55(t)
Spontaneous echocardiographic contrast ("smoke"), 167, 636–637, 661
hypertrophic cardiomyopathy and, in cat, *633*
Springer spaniel. See also *Dog(s).*
atrioventricular myopathy in, pathology of, *837*
dilated cardiomyopathy in, *583*
echocardiography in, ventricular septal defect on, *502*
St. Bernard. See also *Dog(s).*
dilated cardiomyopathy in, *583*
radiography in, rounded-chest conformation on, *109*
Standstill, atrial. See *Persistent atrial standstill (atrioventricular myopathy).*
Stenosis, valvular, 158–159
echocardiographic findings associated with, 159–160
in cat, *136*
in dog, *136*, 159, *159*, 160, *160*
sites of. See *Aortic stenosis; Mitral stenosis; Pulmonic stenosis; Tricuspid stenosis.*
Sternotomy, 867
Steroids, use of, in CPCR, 438
in management of shock, 285
in treating sequelae of heartworm disease, in dog, 714, 716, 718
Stethoscopic examination, 51. See also *Heart murmurs; Heart sound(s).*
electronic, 51
Stiffness, myocardial, 30, *30*, 32
Strength-duration curve, for pacemaker, *404*, 404–405
Streptokinase, adverse effects of, 916(t)
for thromboembolism, in cat, 664, 916(t)
recommended dosages of, for cat, 916(t)
ST segment, 74
significance of changes in, 87, *87*
Subaortic stenosis, 158–159, 485–494
angiocardiographic findings associated with, in dog, *189*
aortic regurgitation accompanying, 492
Subaortic stenosis *(Continued)*
echocardiographic findings associated with, 492
in dog, *490*
canine breed predisposition to, 460, 460(t)
echocardiographic evidence of, 159, 488, *489*, 490
in dog, *136*, 159, *159*, *490*, *491*, *492*
electrocardiographic findings associated with, 490
in dog, *489*
gross morphology of, in cat, 823
in dog, 486–487, *488*, 822–823
heart failure accompanying, treatment of, 228
heart murmur associated with, *60*, 60–61
myocardial fibrosis accompanying, 487–488
echocardiographic evidence of, 488, *489*
prevalence of, in dog, 459(t), 460
radiographic findings associated with, 489
in dog, *491*
surgery for, 872–873
Supraventricular tachyarrhythmias, 96
in cat, 391–393
in dog, 338–347
differentiation of, from ventricular tachyarrhythmias, 332(t), 332–338
P wave and QRS complex in, 333–334, *336*, *337*, *338*
QRS complex morphology in, 333, *333*, *334*, *335*
unreliability of rhythm (ir)regularities and pause length in, 334–335
vagal maneuvers in, 335–336, 338, *339*, *340*
treatment of, 347–355
adverse effects of, 351–352
evidence of drug effectiveness in, on ECG, *349*, *350*, *351*, *353*
Supraventricular tachycardia, 96
in cat, 391, *392*
in dog, *96*, 338–347. See also *Supraventricular tachyarrhythmias, in dog.*
AV node–dependent, 338, 345–347
treatment of, 354–355
AV node–independent, 338–345
treatment of, 348–354
death risk associated with, 348
F waves associated with. See *Fibrillation, atrial, in dog; Flutter, atrial, in dog.*
Surface electrocardiogram, 71
Surgery, 866–880
anesthesia for. See *Anesthesia.*
corrective procedures preceding, 857
for aortic stenosis, 872–873
for arteriovenous fistula, 790–791
for atrial septal defect, 873
echocardiographic findings following, in dog, Plate 9
for cardiac tumors, 880
for caval syndrome, in dog, 879
for cor triatriatum, 878–879
for dirofilariasis, in dog, 714, 879
for endocardiosis, 877
for eosinophilic granulomatosis, in dog with heartworm disease, 718
for heart base chemodectoma, 880
for heart disease, 866–880
for heartworm disease, in dog, 714, 879
for hyperthyroidism, complications of, 787–789

Surgery *(Continued)*
in cat, 787, *788*. See also *Thyroidectomy*.
for left-to-right-shunting patent ductus arteriosus, in dog, 511
complications of, 511, *512*
for mitral regurgitation, 877–878
for patent ductus arteriosus, *876*, 876–877, *877*
in dog, 511
complications of, 511, *512*
recanalization following, 877
for pericardial disease, 879–880
for pericardial effusion, 695
for persistent right aortic arch, 878
for pulmonic stenosis, *869*, 869–872, *871*
for right atrial hemangiosarcoma, 880
for subaortic stenosis, 872–873
for tetralogy of Fallot, 875, *875*
for tricuspid valve lesions, inutility of, 878
for vascular ring anomalies, 878
for ventricular septal defects, 874, *874*
to implant pacemaker, 414(t), 414–415, *415*, 416(t)–419(t)
Swollen abdomen, significance of, 44, 47
Sympathetic effects, of antiarrhythmics, 309(t)
Sympathomimetic amines. See also *Dobutamine; Dopamine.*
for heart failure, 224, 229(t), 233–234
Syncope, 446–453
altered blood constituents and, 447
arrhythmias and, 450–451
electrocardiographic monitoring for, 448–449, *449*
treatment of, 450, 451
bradyarrhythmias and, 451
cardiogenic, 446, 450–452
canine breed predisposition to, 451(t)
carotid sinus hypersensitivity and, 452
cause(s) of, 43(t), 44, 446–447, 450–453
determination of, clinical approach to, 447
differential diagnosis of, 447(t)
drug-related, 453
heart failure and, 451
hypertrophic cardiomyopathy and, 451
in cat, 636
hypotensive, 446
management of, 450–453
neurocardiogenic, 452
neurogenic, 447, 452–453
provocative testing for, using vagal maneuvers, 449–450
via exercise, in dog, 449
reflex, 452
sick sinus syndrome and, in dog, 450
specialized testing for, in man, 450
structural heart disease and, 451–452
tachyarrhythmias and, 450
tussive ("cough drop"), in dog, 453
vasovagal, 452
ventricular underfilling and, 451–452
vs. seizures, 447–448
Systemic hypertension. See *Hypertension*.
Systemic inflammatory response syndrome, 274, 274(t), 275(t)
treatment of, 276(t)
Systemic lupus erythematosus, cardiac manifestations of, 775–776
Systemic sequelae, of infectious endocarditis, 570–571, *571*, 573
Systemic vascular disease, prevalence of, in dog, 467
Systemic vascular resistance, *32*, 33
Systolic clicks, 54
Systolic dysfunction, hypertrophic cardiomyopathy and, 628
Systolic dysfunction *(Continued)*
therapeutic approach to, 218–222
Systolic heart murmurs, 58–61. See also *Heart murmurs*.

T wave, 72, 74
abnormal, 88, *88*
Tachyarrhythmia(s), 96, 98–99. See also *Arrhythmia(s)*.
hyperthyroidism and, in cat, 783(t), 786
hypertrophic cardiomyopathy and, in cat. See under *Arrhythmia(s), hypertrophic cardiomyopathy and.*
supraventricular, 96
in cat, 391–393
in dog, 338–347
differentiation of, from ventricular tachyarrhythmias, 332(t), 332–338
P wave and QRS complex in, 333–334, *336*, *337*, *338*
QRS complex morphology in, 333, *333*, *334*, *335*
unreliability of rhythm (ir)regularities and pause length in, 334–335
vagal maneuvers in, 335–336, 338, *339*, *340*
treatment of, 347–355
adverse effects of, 351–352
evidence of drug effectiveness in, on ECG, *349*, *350*, *351*, *353*
syncope associated with, in cat, 450
in dog, 450
ventricular, 98–99
in cat, 98, 99, 396–398, *397*
in dog, 98, 99, *99*, 355–361
vs. supraventricular tachyarrhythmias. See *Tachyarrhythmia(s), supraventricular, in dog, differentiation of.*
with altered heart sounds, 57
Tachycardia. See also *Tachyarrhythmia(s)*.
atrial, 96
in cat, 391, *392*
in dog, ectopic, *341*, 341–342
treatment of, 350–351
atrioventricular nodal re-entrant, in dog, 345–346, *346*
bypass tract–mediated macro-re-entrant, in dog, 347, 355
dilated cardiomyopathy in relation to, in dog, 587
heart failure due to, in dog, 587
junctional, 97
in dog, 346–347
sick sinus syndrome and, in miniature schnauzer, 355
sinus, 91
in cat, 390
hyperthyroidism and, 90, *90*
in dog, 338–339
sinus nodal re-entrant, in dog, 339, 341
supraventricular, 96
in cat, 391, *392*
in dog, *96*, 338–347. See also *Tachyarrhythmia(s), supraventricular, in dog.*
AV node–dependent, 338, 345–347
treatment of, 354–355
AV node–independent, 338–345
treatment of, 348–354
death risk associated with, 348
F waves associated with. See *Fibrillation, atrial, in dog; Flutter, atrial, in dog.*
Tachycardia *(Continued)*
ventricular. See *Tachyarrhythmia(s), ventricular.*
Tachypnea, 46
Tamponade, cardiac, 689–690
echocardiographic findings associated with, 164
in dog, *165*
pathophysiology of, *689*, 689–690, *690*
pericardial effusion and. See *Pericardial effusion.*
pericardiocentesis for, 694–695
Taurine, 748–749
deficiency of, 748–749
and dilated cardiomyopathy, in cat, 645–646, 750–751
in dog, 585–586, 751–752
supplemental, for cardiomyopathy, in cat, 637, 650, 751, 916(t)
in dog, 596, 916(t)
Temperature regulation, dysfunctional, cardiac manifestations of, 773–774
Temporary atrial fibrillation, in dog, 354
Temporary pacemaker, 408. See also *Pacemaker.*
implantation of, 414(t)
Tendon of Todaro, 22
Terbutaline, adverse effects of, 916(t)
bronchodilation with, 916(t)
for sick sinus syndrome, 450
recommended dosages of, for cat, 916(t)
for dog, 916(t)
Terrier. See also *Dog(s).*
aortic stenosis in, gross morphology of, *488*
dilated cardiomyopathy in, 582(t)
pulmonic stenosis in, echocardiographic findings associated with, *486*
radiographic signs of, *482*
tracheal collapse in, radiographic appearance of, *122*
Tetralogy of Fallot, 515–518
angiocardiographic assessment of, 517
in cat, *514*
in dog, *189*, *514*
radionuclide, *196*
canine breed predisposition to, 462
echocardiographic findings associated with, 160, 517
in dog, *516*
electrocardiographic findings associated with, 517
gross morphology/pathology of, 826
in cat, 826
in dog, 826
prevalence of, in dog, 459(t), 462
surgery for, 875, *875*
Theophylline. See also *Aminophylline.*
adverse effects of, 917(t)
bronchodilation with, 917(t)
recommended dosages of, for cat, 917(t)
for dog, 904(t), 917(t)
Thermoregulatory dysfunction, cardiac manifestations of, 773–774
Thiacetarsamide, for heartworm disease, in cat, 733
in dog, 712, 713, 905(t), 917(t)
Thiazide diuretics. See also specific agents, e.g., *Chlorothiazide; Hydrochlorothiazide.*
for heart failure, 235(t), 236–237
Thiobarbiturates, as anesthetic agents, 861
Third heart sound, 55–56
abnormal, in dog with dilated cardiomyopathy, *56*
Third-degree atrioventricular block, 83–84
in cat, 395, *395*, *401*

Third-degree atrioventricular block (*Continued*)
as indication for pacemaker, 403
in dog, *83*, 375, *401*
as indication for pacemaker, 402
Thoracic cavity, anatomy of, 13–14, *14, 15*
Thoracic compressions, in basic life support, 433–434
factors limiting effectiveness of, 434(t)
Thoracic conformation, on radiography, *109*, 110
Thoracic duct, 22
Thoracic examination, 50
auscultation in, 50–53, *51, 53*. See also *Heart murmurs; Heart sound(s).*
Thoracic inlet, 13
Thoracic organs, removal of, at necropsy, 845–846
Thoracic radiography. See *Radiography.*
Thoracic surgery. See *Surgery.*
Thoracic venous anomalies, 529
Thoracotomy, 868, *869*
emergency, in basic life support, 434–435
Three-dimensional echocardiography, 134
Thromboembolism, 834–835
in cat, 658–667
aorta as site of. See *Embolism, aortic.*
echocardiographic "smoke" (spontaneous contrast) presaging, *633*
limb paralysis or contracture as sequela of, 44, 660, *660, 663*
prevention of, 666–667
renal infarction as sequela of, *661*
therapy for, 663–666
amputation in, 665, *666*
aspirin in, 665, 908(t)
complications associated with, 665, *665*
heparin in, 664, 912(t)
results of, 664
streptokinase in, 664, 916(t)
tissue plasminogen activator in, 664, 917(t)
warfarin in, 664, 917(t)
complications associated with, 665, *665*
in dog, aspirin for, 908(t)
heparin for, 912(t)
as element of therapy for heartworm disease, 713, 715, 719
prevalence of, 467
warfarin for, 917(t)
pulmonary, 761–762
prevalence of, in dog, 467
"smoke" (spontaneous echocardiographic contrast) presaging, 167, 636, 637, 661
in cat, *633*
Thrombogenesis, Virchow's triad in, 658
Thrombolytic therapy. See specific agents cited under *Thromboembolism, in cat; Thromboembolism, in dog.*
Thrombotic endocarditis, nonbacterial, 568
Through-transmission, in ultrasonography, 132
Thyroid gland, functioning of, abnormal, 762–763, 781–789. See also *Hyperthyroidism; Hypothyroidism; Thyrotoxic heart disease*
tests of, in diagnosis of hyperthyroidism, 784
radionuclide imaging of, in diagnosis of hyperthyroidism, 785, *785*
resection of. See *Thyroidectomy.*
Thyroidectomy, in cat, 787, *788*
diminished cardiomegaly following, *784*
Thyroidectomy (*Continued*)
electrocardiographic findings subsequent to, *783, 784*
extracapsular technique of, 787
modified, 787, *788*
hyperthyroidism recurring after, 789
hypocalcemia following, 788–789
electrocardiographic evidence of, *784*
hypoparathyroidism as complication of, 788, 789
hypothyroidism due to, 789
intracapsular technique of, 787
renal failure as complication of, 789
Thyrotoxic heart disease, in cat, 782–789, 830. See also *Hyperthyroidism.*
arrhythmias accompanying, 90, *90*, 388
changes in presentation of, in recent decades, 785
electrocardiographic findings associated with, *83*, 90, *90*, 782–783, *783*, 783(t)
radiographic evidence of, 783, *784*
Thyrotoxicosis. See *Hyperthyroidism; Thyrotoxic heart disease.*
Thyroxine, abnormal secretion of, 762–763, 781–789. See also *Hyperthyroidism; Hypothyroidism; Thyrotoxic heart disease.*
replacement therapy with, in thyroidectomized cat, 789
Ticarcillin, for endocarditis, 577(t)
Tissue perfusion, monitoring of, in CPCR, 440
in management of shock, 267
Tissue plasminogen activator (t-PA), adverse effects of, 917(t)
for thromboembolism, in cat, 664, 917(t)
recommended dosages of, for cat, 917(t)
Tocainide, 318–319
adverse effects of, 315(t), 319, 917(t)
electrocardiographic parameters affected by, 311(t)
for arrhythmias, 318, 917(t)
in dog, 315(t)
in dog with dilated cardiomyopathy, 598
recommended dosages of, for dog, 904(t), 917(t)
Tomography, computed, of heart, *199*, 199–200
Tongue, drug injection in, and CPCR, 436–437
Toxoplasmosis, and myocarditis, in dog, 611
t-PA (tissue plasminogen activator), adverse effects of, 917(t)
for thromboembolism, in cat, 664, 917(t)
recommended dosages of, for cat, 917(t)
Tracheal collapse, radiographic appearance of, 121, *122*
Tracheal suction, in basic life support, 433
Tracheotomy, in basic life support, 429
Tranquilizers, for anxious dog or cat with pulmonary edema, 260, 260(t)
Transcatheter occlusion, of patent ductus arteriosus, 190
in dog, 511, *512*
Transducer, in ultrasonography, 131, 140
esophageal placement of, 132
Transesophageal echocardiography, 132, 134
Transfusion, in anemic animal with heart failure, 790
in management of shock, 279–280
Transient heart sounds. See *Heart sounds.*
Trans-septal approach, to left-sided cardiac catheterization, 180. See also *Cardiac catheterization.*
Transtelephonic electrocardiography, 102
Transtracheal catheter ventilation, in basic life support, 429, 431
Transtracheal drug delivery, in advanced life support, 435–436
Transtracheal oxygen insufflation, in basic life support, 429
Transvenous implantation, of pacemaker, 416(t)–418(t)
Triamterene, adverse effects of, 917(t)
for heart failure, 235(t), 237, 917(t)
recommended dosages of, for cat, 917(t)
for dog, 917(t)
Triangle of Koch, 22
Tricuspid regurgitation, 227–228, 555–558
cardiomegaly accompanying, *114*, 557
heart murmur associated with, 60, 557
Tricuspid stenosis, 823
Tricuspid valve, 20, 556
blood flow in or across, Doppler-derived velocity of, in cat, 154(t)
in dog, 154(t)
regurgitant. See *Tricuspid regurgitation.*
dysplasia of, 158, 524–526
angiocardiographic findings associated with, 525
canine breed predisposition to, 461–462
echocardiographic findings associated with, 158
in dog, *158*
electrocardiographic findings associated with, 525
in dog, *524*
prevalence of, in dog, 459(t), 461–462
radiographic findings associated with, 525
in dog, *114, 523*
hematocysts in, prevalence of, in dog, 463–464
stenosis of, 823
surgery of, inutility of, 878
Truncus arteriosus, 519
lesion mimicking, *513, 516*, 520
Trypanosomiasis (Chagas' disease), and myocarditis, 833
in dog, 611, *611, 833*
in dog, 611
and myocarditis, 611, *611, 833*
Tumor(s), aldosterone-secreting, 765
cardiac, 120, 679, 698–699, 836
and pericardial effusion, 686, 695
in cat, 657, *657, 688*, 698–699, 836
echocardiographic findings associated with, *694*
prevalence of, 467
in dog, 610, 686, *687, 688*, 698
echocardiographic findings associated with, *166*, 693, *694*
prevalence of, 466
radiographic findings associated with, *692*
surgery for, 880
catecholamine-secreting, 765–766
chemotherapy for, cardiotoxicity of, in cat, 657
in dog, 609
Turbulent blood flow, 137
Tussive syncope ("cough drop" syncope), in dog, 453
Twenty-four hour ambulatory monitoring (Holter monitoring), 102, *102*. See also *Electrocardiography.*

Twenty-four hour ambulatory monitoring (Holter monitoring) *(Continued)*
for arrhythmias and syncope, 448, *449*
for canine arrhythmias, 331–332. See also *Dog(s), electrocardiography in.*
Two-dimensional echocardiography, 132. See also *Echocardiography.*
advantages of, 132
aortic stenosis on, *489*
in dog, 159, *159, 492*
cardiac tamponade on, in dog, *165*
cardiac tumor on, in cat, *694*
in dog, *694*
cardiomyopathy on, 162, 163
chronic acquired valvular disease on. See *Two-dimensional echocardiography, endocardiosis on.*
cor triatriatum on, in dog, *527*
dilated cardiomyopathy on, 162
in dog, *593*
dirofilariasis-related changes on, in cat, *733*
in dog, *711*
disadvantages of, 132
Duchenne's cardiomyopathy on, in dog, *607*
endocardiosis on, 161
in dog, *161*
mitral regurgitation accompanying, 161
in dog, *161*
evidence of endocarditis on, in dog, *164*
heartworm-related changes on, in cat, *733*
in dog, *711*
hypertrophic cardiomyopathy on, 163
in cat, *626, 627, 629*
in dog, *606*
imaging planes for, 141–142, *141–144*
intrapericardial cyst on, in dog, *686*
left-to-right shunt on, patent ductus arteriosus and, in dog, *156, 510*
mitral regurgitation on, endocardiosis and, 161
in dog, *161*
in cat with hypertrophic cardiomyopathy, *627*
muscular dystrophy–related myocardial lesions on, in dog, *607*
myocardial diseases on. See *Two-dimensional echocardiography, cardiomyopathy on.*
myocardial fibrosis on, aortic stenosis and, *489*
patent ductus arteriosus on, in dog, *156, 510*
pericardial cyst on, in dog, *686*
pericardial effusion on, in dog, *165, 693*
pleural effusion on, in cat, *165*
in dog, *165, 693*
pulmonic stenosis on, 159
in dog, *160*
restrictive cardiomyopathy on, in cat, *643*
spontaneous contrast ("smoke") on, in cat with hypertrophic cardiomyopathy, *633*
subaortic stenosis on, *489*
in dog, 159, *159, 492*
tetralogy of Fallot on, 160
in dog, *516*
valvular disease on, chronic acquired. See *Two-dimensional echocardiography, endocardiosis on.*
valvular stenosis on, in dog, 159, *159, 160*
vegetative mass on, endocarditis and, *164*
ventricular septal defect on, in dog, *157, 502*
Two-dimensional ultrasonography, abdominal, signs of heart failure on, in dog, *153*
cardiac. See *Two-dimensional echocardiography.*

Ultrasonography, 130–132
abdominal, signs of heart failure on, 153
in dog, *153*
cardiac. See *Echocardiography.*
transducer in, 131, 140
esophageal placement of, 132
Unipolar pacemaker, 409, *410.* See also *Pacemaker.*
Uremia. See *Kidney(s).*

Vagal maneuvers, in diagnosis of arrhythmias, in cat, 389
in differentiation of tachyarrhythmias, in dog, 335–336, 338, *339, 340*
in provocative testing for syncope, 449–450
Valve conduits, in surgery for aortic stenosis, 873
Valve(s) of heart, *19,* 20–21. See also specific valves, e.g., *Mitral valve.*
acquired disease of, 536–559. See also *Endocardiosis.*
in cat, 462, 463
in dog, 463(t), 463–464
blood flow in or across, Doppler-derived velocity of, in cat, 154(t)
in dog, 154(t)
regurgitant, quantification of, via Doppler echocardiography, 154
sites of. See *Aortic regurgitation; Mitral regurgitation;* etc.
congenital disease of, in cat, 462, 463
in dog, 459(t)–461(t), 460–462, 463(t)
development of, 6, *6*
defective, 6
dysplasia of, 158
echocardiographic findings associated with, 158
in dog, *158*
sites of. See site-specific sub-entries under *Dysplasia.*
stenosis of, 158–159
echocardiographic findings associated with, 159–160
in cat, *136*
in dog, *136,* 159, *159,* 160, *160*
sites of. See *Aortic stenosis; Mitral stenosis; Pulmonic stenosis; Tricuspid stenosis.*
vegetations on, in IE, 163, 567–568, *569.* See also *Infectious endocarditis.*
echocardiographic appearance of, *164,* 573, *574*
in dog, *164*
Valvuloplasty, balloon, for pulmonic stenosis, 190, 868
Valvulotome valvotomy, for pulmonic stenosis, 870
Vascular disease, pulmonary, prevalence of, in dog, 467
systemic, prevalence of, in dog, 467
Vascular resistance, systemic, *32,* 33
Vascular ring anomalies, 120–121, 528, 826
surgery for, 878
Vasodilators, 237–238. See also specific agents, e.g., *Hydralazine.*
Vasodilators *(Continued)*
for heart failure, 223–224, 237(t), 237–243
in dog with mitral regurgitation, 552
for hypertension, 807
for pulmonary edema, 260, 260(t). See also *Vasodilators, for heart failure.*
for shock, 283(t), 283–284
recommended dosages of, for cat, 904(t)
for dog, 904(t)
Vasopressor impulses, 33(t)
Vasovagal syncope, 452
Vaughan-Williams classification, of antiarrhythmics, 307, 308, 309(t), 310
Vectorcardiography, 70, *70*
Vegetations, on heart valves, in IE, 163, 567–568, *569,* 570. See also *Infectious endocarditis.*
echocardiographic appearance of, *164,* 573, *574*
in dog, *164*
Velocity, of blood flow. See *Blood flow; Doppler echocardiography, blood flow velocity derived from.*
of sound waves, 131
Vena cava, caudal, 17
radiographic appearance of, interpretation of, 120
cranial, 17
persistent left cranial, 529
in dog, *529*
Vena caval syndrome, in dog with heartworms, 718–719
surgery for, 879
Venous anomalies, thoracic, 529
Ventilation, in basic life support, 431–433
in management of shock, 275
Ventricle(s) of heart, 17, 19–20. See also *Ventricular* entries.
compliance of, 30, *31, 217,* 217–218
formation of, 4
function of, radionuclide angiocardiography in evaluation of, 195–199, *197,* 197(t), *198*
growth of, 9, *9*
hypertrophy of. See *Hypertrophy, ventricular.*
interdependence of, 32
left. See *Left ventricle.*
opening of, at necropsy, 846
right. See *Right ventricle.*
septum between, 15, 20
defect in. See *Ventricular septal defect.*
formation of, 4–5, *6*
sequential contractions of atria and, in cardiac pacing, 411, 412
thickness of walls of, measurement of, 847–848
underfilling of, and syncope, 451–452
Ventricular arrhythmias, 98–99
in cat, 98, 99, 396–398, *397*
in dog, 98, 99, *99,* 355–361
lethality of, 356–357, 370, 836
vs. supraventricular arrhythmias. See *Tachyarrhythmia(s), supraventricular, in dog, differentiation of.*
mechanisms for, electrophysiologic, 296(t)
Ventricular asystole, 99–100
Ventricular extrasystoles, 97–98
in cat, 396, *396,* 397, 398
in dog, *98*
breed predisposition to, 466
Ventricular fibrillation, 99, *99*
bretylium for, 909(t)
countershock for, 438–439

Ventricular flutter, 99
Ventricular pacemaker implantation, 416(t)–417(t), 419(t). See also *Pacemaker.*
Ventricular pre-excitation, 86–87
in cat, *393,* 393–394
in dog, *86*
Ventricular septal defect, 156–157, 499–505
angiocardiographic findings associated with, 505
in dog, *189, 501, 502*
radionuclide, 194, *195*
in dog, *194*
canine breed predisposition to, 461, 461(t)
echocardiographic evidence of, 156–157, 503–504
in dog, *157, 501, 502, 504,* Plate 6
electrocardiographic findings associated with, 503
in dog, *504*
gross morphology/pathology of, 501, 825
in cat, *500*
heart murmur caused by, 61
lesions accompanying, in tetralogy of Fallot. See *Tetralogy of Fallot.*
nonrestrictive, 157
prevalence of, in dog, 459(t), 461
radiographic findings associated with, 503
in dog, *503*
restrictive, 157
shunt(ing) accompanying, 157
echocardiographic findings associated with, in dog, *504*
indicator dilution in identification of, *186*
surgery for, 874, *874*
Ventricular tachyarrhythmias, 98–99
in cat, 98, 99, 396–398, *397*
in dog, 98, 99, *99,* 355–361
vs. supraventricular tachyarrhythmias. See *Tachyarrhythmia(s), supraventricular, in dog, differentiation of.*
Ventricular underfilling, and syncope, 451–452
Ventriculoatrial conduction, as complication of cardiac pacing, 412, *413,* 414
Verapamil, 324–325
adverse effects of, 315(t), 325, 917(t)
drugs interacting with, effects of, 326(t)
for arrhythmias, 324, 917(t)
in dog, 315(t), 348, 349
evidence of effectiveness of, on ECG, *350*
for hypertension, 805(t)
for supraventricular tachycardia, in dog, 348, 349
evidence of effectiveness of, on ECG, *350*
recommended dosages of, for dog, 903(t), 917(t)
Viral infection, dilated cardiomyopathy due to, in man, 586
myocarditis due to, 833
in dog, 610–611, 832
Virchow's triad, in thrombogenesis, 658
Visceral pericardium (epicardium), 14, 15, 679, 680. See also *Pericardial* entries.
Viscosity, of blood, 33
increase in, cardiac manifestations of, 772–773
Volume of distribution, of drugs, 312–313
Volume overload, 220
patent ductus arteriosus and, 209–210, *210*
response to, 209–210
in form of eccentric myocardial hypertrophy, 208, 757, 818
VSD. See *Ventricular septal defect.*

Warfarin, adverse effects of, 917(t)
for thromboembolism, in cat, 664, 917(t)
complications associated with, 665, *665*
in dog, 917(t)
recommended dosages of, for cat, 917(t)
for dog, 917(t)
Wavelength, of sound, 131
Weakness, causes of, 44
episodic, 446. See also *Syncope.*
canine DCM and, electrocardiographic findings associated with, *449*
differential diagnosis of, 447(t)
Weight. See *Body weight.*
Welsh corgi. See also *Dog(s).*
M-mode echocardiography in, normal findings on, 145(t)
West Highland terrier. See also *Dog(s).*
echocardiography in, pulmonic stenosis on, *486*
Whole blood, in management of shock, 279–280
Wolff-Parkinson-White syndrome, 86
Wolfhound. See also *Dog(s).*
Irish, dilated cardiomyopathy in, 582(t), *583*
M-mode echocardiography in, normal findings on, 145(t)
Work overload. See *Overload.*
Worm infestation, in pulmonary arteries and heart. See *Heartworm disease.*

X-linked muscular dystrophy, in dog, 606–607, 832
myocardial lesions associated with, 607, *607*
Xylazine, as preanesthetic agent, 859(t), 860

Yorkshire terrier. See also *Dog(s).*
tracheal collapse in, radiographic appearance of, *122*

Z bands, around sarcomere, 29

ISBN 0-7216-4044-3